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SYSTEMIC BLASTOMYCOSIS.

ITS ETIOLOGIC, PATHOLOGIC AND CLINICAL FEATURES AS ESTABLISHED BY A CRITICAL SURVEY AND SUMMARY OF TWENTY-TWO CASES, SEVEN PREVIOUSLY UNPUBLISHED; THE RELATION OF BLASTOMYCOSIS TO COCCIDIOIDAL GRANULOMA.*

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AND
OLIVER S. ORMSBY, M.D.
CHICAGO.

Since Gilchrist, in America, and Busse and Buschke, in Germany, first described the infectious disease now generally known as blastomycosis, about one hundred cases involving the skin have been recognized, chiefly in Chicago and its vicinity, but also in other parts of the United States, in Canada, in various parts of Europe, in Japan, India and South America. In consequence cutaneous blastomycosis is generally accepted by dermatologists and pathologists throughout the world as a distinct clinical and pathologic entity.[1]

It is not, however, so generally understood that deeper-seated infection with these same organisms may cause grave and usually fatal systemic disease. The purpose of this paper is to call attention to a number of recorded and unrecorded cases of systemic blastomycosis and to summarize and classify, as far as is now possible, the etiologic, pathologic and clinical features of the disorder. We have collected twenty-two cases (seven not yet published[2]) in which the diagnosis of systemic blastomycosis has been demonstrated beyond question by histologic and bacteriologic

*Read before the Sixth International Congress of Dermatology, New York, Sept. 8-14, 1907. The authors acknowledge the use of the following illustrations: Figs. 2, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15 and 16 from the Journal of Cutaneous Diseases. Figs. 2, 4, 12 and 13 from The Journal of the American Medical Association, June 7, 1902.

1. A general discussion of cutaneous blastomycosis, with a summary of the clinical, pathologic and bacteriologic features of the disease, with 16 clinical illustrations and 25 illustrations of the histology and bacteriology, is given in a paper by Montgomery, Jour. Am. Med. Assn., June 7, 1902; a brief summary in Hyde and Montgomery's Diseases of the Skin, ed. 7; a general summary by Gilchrist, Brit. Med. Jour., 1902, p. 1321; and original reports of many cases since January, 1900, in Jour. Cutan. Dis., and other journals.

2. Four or five of these will be published in full later by some of our Chicago colleagues, who have kindly permitted us to make abstracts from their notes.

study of the lesions, and in eleven instances by autopsy. To the reports of the twenty-two unquestionable cases on which this paper is based we have added brief notes of five other cases in which blastomycetes were demonstrated in local lesions or in the sputum, and in which all clinical signs pointed to systemic infection, but in which the final proof of such infection is wanting.

HISTORY AND GEOGRAPHIC DISTRIBUTION.

The cases in the appended summary are arranged in order of publication. Busse and Buschke's case of cutaneous and systemic blastomycosis was first reported by Busse in 1894, a few weeks after Gilchrist had demonstrated before the American Dermatological Association his sections from a cutaneous lesion. The Curtis case was published in 1896. The first American case of systemic blastomycosis (No. 3) was under observation in 1894-5, but its true nature was not discovered until five years later through examination of the sections and tissue which had been preserved. Sixteen of the cases herewith tabulated have been recorded within the last two years.

The residences of the 22 patients at the time of acquiring the disease were, as nearly as can be determined, as follows: Chicago, 13; Iowa, 2; Indiana, Wisconsin, Ohio, Maryland, New York City, Germany and France, 1 each. The Wisconsin patient probably acquired his disease while working in one of the southern states. The true nature of the Indiana, Wisconsin and Ohio cases was discovered when the patients were in Chicago for examination and treatment. Though it is evident that blastomycosis, both cutaneous and systemic, occurs most frequently in Chicago and its vicinity, it is probable that one reason why so many reports come from this city lies in the fact that a number of Chicago physicians have become familiar with the disorder and are on the lookout for it.

ETIOLOGY.

Predisposing causes, aside from those which favor any infection, can not be recognized in the study of the twenty-two cases. Family and personal histories are, in the main, negative. There is no evidence of inheritance or contagion, though in one of the doubtful cases (29) there were two, and possibly three, individuals of the same family with lesions showing infection with blastomycetes. Of the twenty-two patients, nineteen were males and three females. The ages varied from 17 to 58, seventeen patients being between 20 and 47, the period usually of greatest activity and consequently of most frequent exposure to infections. The

occupation of sixteen of the nineteen men is given as follows: laborers, 7; farmers, 3; machinists, 2; engineer, carpenter, policeman and convict, 1 each. Of the three women, one was occupied on a farm, one was a German housewife, the other was a young married woman with no occupa-

Figs. 1, 2, 3 and 4.—Characteristic lesions of cutaneous blastomycosis. Fig. 4 shows also metastatic lesions. (From Case 3.)

tion. The hygienic surroundings and financial condition of the patients were unfavorable in the majority of cases.

The active and essential cause of the disease is infection with organisms which, for the want of a more exact and satisfactory term, are desig-

nated as blastomycetes. That these organisms are the pathologic factors in these cases has been clearly demonstrated, first, by finding the organisms in pus and tissue; second, by obtaining them in pure culture from subcutaneous abscesses and at autopsies from miliary nodules and abscesses of internal organs, and, third, by reproduction of the disease in guinea-pigs and other animals after inoculation with pure cultures, and recovery of the organism in pure cultures from the generally disseminated lesions in these animals (Cases 1, 2, 4, 5, 8, 9, 14 and 18). The organism is a distinct pus-producer and is readily obtained in pure culture from any of the unbroken abscesses.

Fig. 2.

Tuberculosis has been excluded from all the cases by examination of secretions and tissues. In Cases 1, 2, 3, 5, 7, 8, 9, 12, 14 and 18, a thorough search was made for any possible complicating tuberculosis, not only by the examination of secretions and tissues, but also by the inoculation of guinea-pigs, while in Cases 5, 7 and 14 the tuberculin test and cultures were also employed. Only in Case 11, in which, late in the disease, tubercle bacilli were found in the sputum, was any such complication detected. It is true that in Case 3, after prolonged search, three or four bacilli with staining qualities like those of tubercle bacilli were seen in sections of a small open ulcer of the skin, but the exact nature of these bacilli was not demonstrated, and they were undoubtedly present as the

result of secondary infection, since several guinea-pigs inoculated with tissue from these same lesions did not develop tuberculosis.

The indications concerning the infection atrium and mode of dissemination are as follows: At each of the eleven autopsies the lungs were found to be more or less extensively involved; in several instances with bronchopneumonia. In a number of cases the earliest symptoms were pulmonary, and blastomycetes were demonstrated in the sputum.

Fig. 3.

These facts would point to the respiratory tract as a common point of infection, through the inhalation of particles of dust carrying the organisms. In Cases 3 and 4 typical cutaneous lesions had existed for seven and four years, respectively, before systemic infection occurred. In Case 12 there is a history of a wound of the foot, with the first manifestations of the disease appearing in the adjacent tissues. In the majority of the

cases, however, and especially in those in which the first symptoms were indolent subcutaneous abscesses, the point of inoculation can not be determined.

That the mode of extension is the same as in other pyemias, through the blood instead of by way of the lymphatics, is evident from the wide and often rapid dissemination of deep-seated lesions with little or no involvement of the lymph glands, and from the fact that blastomycetes have been demonstrated in the blood in Cases 4 and 19 and in sections of blood vessels in a number of instances. Enlarged lymph glands are noted clinically in Cases 1, 4, 5, 7 and 19 and at the autopsy in Cases 1, 7, 8, 14, 19 and 20, but in no instance was the involvement of lymph glands a prominent feature.

The organisms are apparently identical with those found in cutaneous blastomycosis and, as these have been described fully and repeatedly, the subject will be considered very briefly here. In unstained preparations of pus and tissue the organisms appear as round or oval bodies with a double-contoured, highly refractive capsule. Within the capsule, in many instances, granules, or spore-like bodies, can be distinguished. The addition of a 1 to 10 per cent. solution of potassium hydrate to the specimen under examination facilitates the recognition of these bodies. In stained sections the double-contoured, homogeneous capsule is usually separated from a finely or coarsely granular protoplasm by a clear space of varying width. Vacuoles of different sizes are found in some organisms. In both pus and tissue, organisms in pairs or in various stages of budding are commonly seen. The parasite, as a rule, varies in size from seven to twenty microns, though slightly smaller and much larger forms occur in some cases.

The organisms are readily obtained in pure culture from unbroken abscesses, from miliary abscesses in the borders of the cutaneous lesions, and from the miliary nodules and abscesses in the deep-seated organs. Cultures were obtained in all the cases here reported, except 3 and 6, in which the nature of the disease was discovered by histologic examination of tissues after death. The parasites grow well on glycerin and glucose agar, blood serum, broth, and other ordinary culture media. A macroscopic growth is usually seen in from two to fourteen days; in subcultures from thirty hours to fourteen or more days. The gross and microscopic forms of the organism in any one case may be made to vary widely with the media employed, and with the temperature and other conditions of growth. As a rule, the growth is more or less moist on glycerin agar, but dry and showing abundant aerial hyphæ on glucose agar. At room temperature there is a greater tendency on all media to a drier growth and a

FIG. 4.

greater development of aerial hyphæ than in the incubator, where the growth is commonly more moist and pasty. Moist growths on glucose agar, taken from the incubator and grown at room temperature, become dry and develop abundant aerial hyphæ. Old cultures on glycerin agar usually present a rough, granular or angleworm appearance of a light brown color.

Microscopically, the bacterium obtained in room-temperature cultures appears at first as a fine branching mycelium with a few small, spore-like bodies. Later, a large, segmented, often pod-like mycelium appears, together with large, round or oval bodies with bud-like projections. Many small spore-like bodies are frequently seen within the larger mycelium and large round bodies, or in groups near a ruptured capsule, but the development of these small bodies into adult forms has not been demonstrated. Cultures grown in the incubator usually show at first budding forms, apparently identical with those seen in tissue and in pus.

The cultural features of the organisms as reported by different observers in different cases have varied considerably. It does not follow, however, that the parasites varied as much as the reports would imply, for with the organism from a single case we have produced practically all the morphologic varieties previously described by ourselves and others. The futility of any attempt to form a classification based on morphology alone is thus apparent. The number and varieties of pathologic fungi of this group can be determined only by a comparative study of them all on uniform lines and with absolutely the same technic.[3] As it has been demonstrated that there are a number of yeasts pathogenic for animals, and as Hanson has shown that yeasts rarely occur singly in Nature, but rather in groups of two or more, it is quite possible that in the majority of cases of blastomycosis there may be present two or three varieties of a given species. Such a hypothesis would explain some of the cultural and other phenomena we have observed.

PATHOLOGY.

Aside from the marked tendency to pus formation, the gross pathology of systemic blastomycosis so closely resembles that of tuberculosis that, in some of the earlier autopsies, the presence of large numbers of minute nodules in different organs led to a macroscopic diagnosis of miliary tuberculosis. The formation of multiple abscesses (especially subcutaneous abscesses) with the resulting sinuses, ulcers and scars, is, however, one of the characteristic features of the disorder. These ab-

3. This has been done with the organisms from four cases, by Hamburger: Jour. Infect. Dis., 1907, iv, 201.

scesses may be microscopic in size, or they may be large enough to hold a liter of pus. They may burrow deeply, involving the muscles, laying bare the tendons, causing erosion and caries of bones and invading the joints, or their origin may be in deeper tissues, producing large thoracic, abdominal or pelvic abscesses. Multiple miliary or pea-sized and larger abscesses may occur in any or all of the organs of the body, but are especially common in the lungs and spleen, which in some instances are completely riddled and largely destroyed. In several instances vertebræ, and in one case several inches of the spinal cord, have been completely de-

Figs. 5 and 6.—Multiple cutaneous lesions such as occur commonly in systemic blastomycosis. (From Case 5.)

stroyed. The bone involvement may occur as a blastomycotic osteomyelitis, as shown in Case 19.

The histologic appearances also strongly suggest those of tuberculosis, but again differ from them, especially in the abscess formation and in the presence in the nodules of greater numbers of polymorphonuclear leucocytes. A small nodule in the lung, which closely resembles in appearance a miliary tubercle, is seen to have the following component parts: In its center is a necrotic mass surrounded by giant cells, outside of which is a

zone of granulation tissue. The necrotic center contains blastomycetes, polymorphonuclear leucocytes, red blood corpuscles and desquamated epithelial cells. Surrounding this mass are varying numbers of giant cells of the Langhans type and embryonic connective-tissue cells. The giant cells nearly all contain blastomycetes in varying numbers, sometimes being crowded full of them. Outside of this area are found plasma, and small, round cells, some connective-tissue fibers and distended capillaries. In these areas the alveolar walls are often not demonstrable, and, in the bronchioles, desquamated epithelial cells, blastomycetes, cellular detritus and pigment are found. In some sections all that remains to show the former presence of bronchioles is the deposit of peribronchial coal dust. At a distance from the blastomycotic bronchopneumonic process, edema of the lung tissue occurs. In cases where greater destruction has ensued, as a result of more active multiplication of the organisms, the identity of the lung tissue is practically lost, its place being occupied by great numbers of the parasites, giant and other cells peculiar to the granulomata, cellular detritus, and large amounts of pigment. The peribronchial lymph nodes contain blastomycotic nodules, similar to those described above, sections of which show less advanced areas of necrosis, surrounded by granulation tissue. The giant cells at times contain pigment as well as the usual organisms.

The smaller areas in the spleen, kidneys, pancreas, adrenals, etc., show, as a rule, collections of blastomycetes and necrotic tissue, the necrosis being less marked than in the lungs, and giant cells less frequent. No giant cells have yet been noted in the spleen. Necrotic areas in bones, containing the organism in abundance, surrounded by leucocytes, giant cells, and other cells peculiar to the granulomata, have been observed in several instances and fully described in Case 8.

In the deeper abscesses (retropharyngeal, deep subcutaneous, etc.), sections from the lining of the abscess cavities show necrotic tissue, blastomycetes, and leucocytes, chiefly polynuclear, surrounded by giant cells, small round cells and fibroblasts, the giant cells all containing blastomycetes.

Sections from a deep unruptured nodule in the skin showed its metastatic origin. It was a beginning abscess situated chiefly in the hypoderm, the overlying epidermis being unaltered. The upper part of the corium showed little change, while in the lower part some edema and moderate degeneration of the collagen was present. In the hypoderm the nodule presented in its center blastomycetes, in groups, in pairs and singly, polymorphonuclear leucocytes and red blood cells. Surrounding this were numerous giant cells of the Langhans type, plasma and connective-tissue

cells. At the margins were some fibroblasts. The giant cells here all contained the organisms.

While as a rule there appears to be a certain amount of uniformity in the arrangement of the component parts of this granuloma in different parts of the body, many sections have no such arrangement, but rather an indefinite commingling of the various cells with the blastomycetes. Ordinary fixing and staining methods suffice to demonstrate the organisms, which are found both within the giant cells and free. Hematoxylin-eosin, polychrome-methylene blue, and Loeffler's alkaline methylene blue are most commonly employed. Metachromism is at times shown by the granules in the organisms when metachromatic stains are employed.

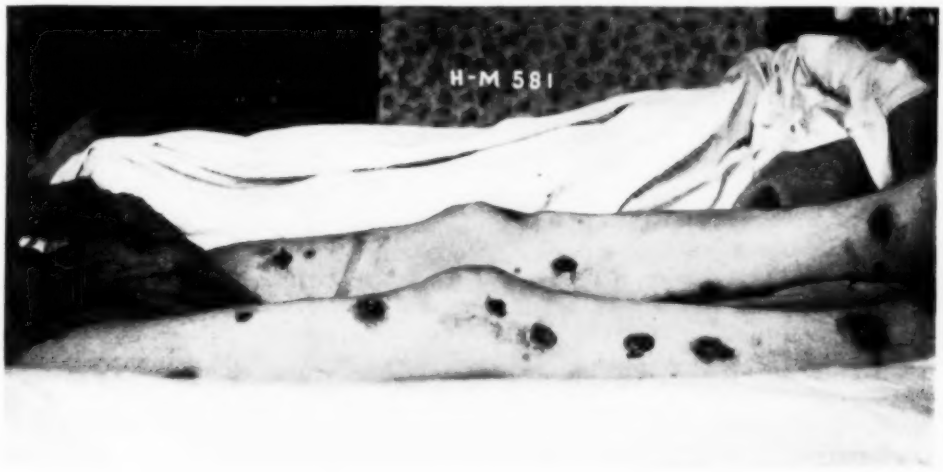


Fig. 6.

It is worthy of note that, notwithstanding the presence of suppuration in all of the cases, in three only (5, 6 and 8) was amyloid degeneration recognized, and in only one instance (Case 8) were these changes at all extensive. In this case amyloid was noted in the spleen, liver, kidneys, adrenals, retroperitoneal and mediastinal lymph nodes and colon.

In ten[4] cases of which full autopsy reports are available, lesions dis-

4. In one (Case 18) of the eleven which came to autopsy we have only the authority of Dr. Evans' oral statement that blastomycotic lesions were distributed generally throughout the body and that several vertebræ and a portion of the spinal cord were destroyed.

tinctly blastomycotic in character were demonstrated in the following organs and tissues: Lungs, in all cases; pleura, in Cases 5, 7, 19 and 20; larynx, in Case 5; trachea and bronchi, in Cases 5, 7 and 8; thyroid cartilage, in Case 9; retropharyngeal and subpleural tissues, in Case 7; myocardium, in Case 6; cerebrum and cerebellum, in Cases 7 and 19; spinal cord, in Case 18; external spinal dura, in Case 7; spleen, in Cases 1, 3, 5, 6, 9, 14, 19 and 20; liver, in Cases 3, 5, 6 and 7; kidney in Cases 1, 3, 5, 6, 7, 9, 19 and 20; adrenals, in Case 6; pancreas, in Case 5; colon, in Case 7; appendix vermiformis, in Case 14; prostate, in Cases 19 and 20; psoas and other deep abscesses, in Cases 8, 9 and 14; bones, not including spinal column, in Cases 1, 7, 8, 9, 19 and 20; spinal column, in Cases 7, 8, 18 and 19; joints, in Cases 7, 18 and 19; lymph nodes, in Cases 7, 8, 14, 19 and 20; muscles, in Cases 19 and 20. Cultures of the blastomycetes were obtained from the pericardial and pleural cavities in Case 20; from the blood in Cases 1 and 19; organisms were demonstrated in sections of blood vessels in Cases 5, 8 and 9.

The blastomycotic nature of the subcutaneous abscesses was demonstrated in each case by cultures or examination of smears. The histology of a subcutaneous nodule is described in detail in Case 5. Sections of many of the cutaneous ulcers were made, showing the characteristic features of cutaneous blastomycosis.

Among other morbid conditions noted at autopsy in these various cases were the following: laryngitis, adenoma of the thyroid, colloid goiter, fibrous and serofibrinous pleuritis, purulent bronchitis, bronchopneumonia, pulmonary edema, fibroid induration of the lungs, pericarditis, atrophy of the heart, perihepatitis, parenchymatous degeneration, fatty changes, adenoma, angioma and atrophy of the liver, nephritis, retention cysts of the kidney, hyperplastic splenitis, atrophy of the testicles, and tigrolysis of ganglion cells of the cerebral cortex and ventral horns of the cord.

Animal experiments have demonstrated the pathogenicity of blastomycetes for guinea-pigs, white mice, rats, rabbits and dogs. The inoculations were far from uniformly successful, many animals showing little or no reaction, and in the experiments that were successful a very large dosage was required. The best results followed intraperitoneal and intravenous injections of pure cultures, and were most marked in those animals killed about three weeks after inoculation. Several guinea-pigs in which a general systemic infection was indicated by irregular fever, lasting a number of weeks, by loss of weight, and even by the formation of palpable abdominal tumors, eventually made a complete recovery, showing their ability to overcome the disease. Local lesions induced by

subcutaneous inoculation usually healed in a few weeks. The gross and microscopic findings in animals were similar to those found in man. In the various animals the following structures showed blastomycotic ulcers, nodules, military tubercles and abscesses: the skin and subcutaneous tissue, lungs, pleura, diaphragm, liver, spleen, kidneys, mesentery, omentum and testicles; mediastinal, mesenteric and inguinal lymph glands, and in one instance the placenta. The involvement to a marked degree of the testicles after intraperitoneal inoculation corresponds to results obtained with the organisms of coccidioidal granuloma after similar inoculations.

Fig. 7.—Cutaneous section showing area of infiltration beginning in hypoderm. (From a subcutaneous nodule, Case 5.)

CLINICAL FEATURES.

The common and most pronounced feature of all the cases (except Case 6, in which there was but one abscess) has been the formation, sooner or later, of multiple abscesses in various parts of the body, with the accompanying symptoms of a chronic pyemia in the form of an irregular, moderate fever, malaise, loss of strength and emaciation. In addi-

tion, many of the cases have presented symptoms due to the location of the disease in certain definite organs, as the lungs or kidneys. In such instances the symptoms closely resemble those of tuberculosis of the same organs, except that the symptoms and clinical signs appear to be even less pronounced than in tuberculous changes of equal extent and severity.

In nine cases (1, 2, 3, 4, 9, 12, 13, 17 and 21) subcutaneous abscesses or local ulcers were the first definitely recognized manifestations of the disorder, and were followed in the course of days or weeks by the development of general symptoms. Evidences of systemic disturbance preceded the appearance of local lesions for periods varying from a few days to a month in five cases (3, 10, 11, 16 and 19), and from three to six months in seven cases (5, 7, 8, 14, 15, 20 and 22). In Case 6 the patient died after about six months of a systemic disorder pointing to involvement of the lungs and intestines and with the development of but a single abscess.

The general symptoms may be ushered in by acute febrile disturbances (as in Cases 3, 10 and 11), by symptoms of a "cold" (as in Cases 5, 6 and 19), by tonsillitis and pneumonia (in Case 15). In fourteen cases the general symptoms were gradual and insidious in their development. In Case 3 there were repeated attacks of an acute febrile condition resembling pneumonia, followed in a few days by the appearance of subcutaneous nodes and abscesses. In several other cases, similar though less pronounced febrile reactions, preceded the appearance of each new crop of abscesses.

The course of the disease is essentially chronic, though moderately acute exacerbations and remissions may occur. In every case, except No. 4, in which the disorder was recognized early and the patient promptly recovered, gradually increasing loss of strength, with emaciation, has been the rule, together with an irregular temperature ranging from normal or subnormal to 101 or 103. Night sweats and edema were features in a number of cases. Death has resulted usually from gradual exhaustion due to the chronic pyemia, or to the general dissemination of the disease through various organs and tissues of the body. In a few instances a fatal termination has been hastened by the rapid and extensive destruction of tissue in the lungs (as in Cases 3 and 5), or in the lungs and other organs (as in Cases 6, 19 and 20). The duration of the disease, aside from Case 4, in which apparent recovery took place in about six weeks, varied from four to six months in four cases (6, 12, 19 and 20), from six months to a year in three cases (3, 5 and 9), and from one to two and one-half years in thirteen cases.

Pulmonary symptoms have been present in many of the cases, but have almost invariably been mild during the early part of the disease

and limited usually to cough with expectoration, or a feeling of discomfort in the chest. In a few cases (as in 3, 5, 7, 9 and 19), as the disease progressed, these symptoms became much more pronounced, with blood-stained sputum. Physical findings have not pointed to extensive involvement of the lungs, except in a few cases (9, 19 and 20) toward the end. With one or two exceptions the changes found in the lungs at the autopsy were much greater than were indicated by the symptoms and physical signs. Blastomycetes were demonstrated in the sputum in Cases 7, 8, 9, 12, 19 and 21. Laryngitis, with hoarseness or aphoria, was a persistent symptom in Case 5, and to a lesser degree in two or three other cases.

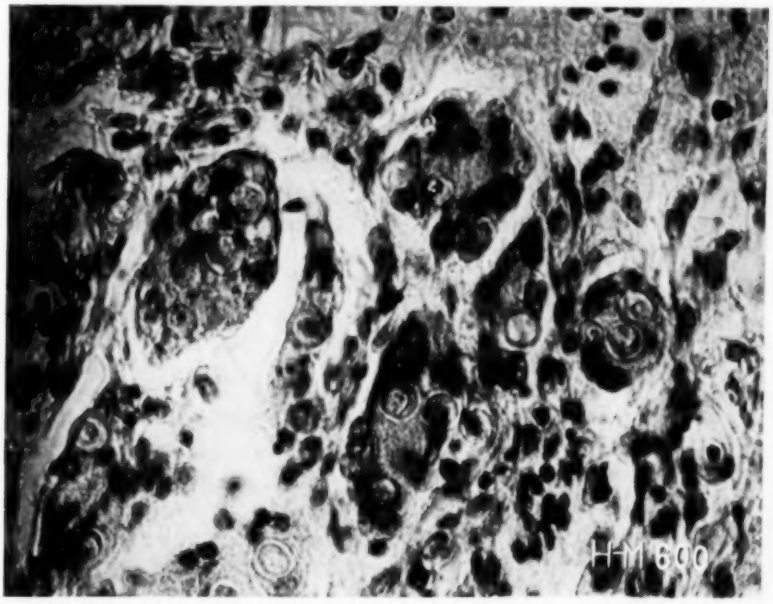


Fig. 8.—Higher magnification of Fig. 7 showing group of giant cells containing the organisms (× 600).

Gastrointestinal symptoms were noted, chiefly in the form of diarrhea, in Cases 6, 7, 8, 12 and 14. Blastomycetes were demonstrated in the feces in Cases 7 and 12. Symptoms of nephritis, with albumin and casts in the urine, were recorded in Cases 6, 7, 8, 9 and 19. Blastomycetes were demonstrated in the urine (from the prostate) in Case 19.

Where blood examination is mentioned, more or less leucocytosis is recorded (in Cases 7, 8, 9, 13, 14, 16, 19 and 21). Anemia was noted in

Cases 5, 8, 16 and 19. Blastomycetes were obtained in culture from the blood in Cases 1 and 19 (they were demonstrated in sections of blood vessels in Cases 5, 8 and 9). Some enlargement of the spleen is noted in Cases 5 and 11; of the liver in Case 5.

The amount of pain experienced by different patients varied widely. With some it was very moderate in both superficial and deep lesions; in others all the lesions, and affected joints especially, were exceedingly painful and sensitive.

The abscesses may be conveniently divided for the purpose of description into two groups, the superficial and the deep. The former appear, usually in considerable numbers and often in successive crops, in different parts of the body as pea-sized or larger, moderately firm nodules in the subcutaneous tissue. The overlying skin is not modified at first, and many of the nodes in the beginning can be detected only by palpation. During periods varying from ten days to several weeks the lesions enlarge, soften and rupture, with the formation of fistulæ, open abscesses or ulcers. Occasional nodes will undergo resolution and disappear after attaining a diameter of one-half an inch or more. Small, unbroken abscesses contain a peculiar glairy muco-pus. As the abscesses get larger, and especially after rupture and secondary infection, the discharge differs little, if at all, from that of an ordinary abscess, though the contents of most of the abscesses are always multiple, from three or four to a dozen or more being present at almost any period of the disease. Ninety-three such abscesses or the resulting lesions of the skin were counted at one time in one patient (Case 5). The deeper abscesses are larger, less numerous, and are usually associated with destructive processes in the bones, muscles and other deep tissues. Psoas, perinephritic, abdominal, thoracic and retropharyngeal abscesses of large size are on record. Superficial abscesses at the time of rupture vary in size from one-half to two inches in diameter. From some of the deep abscesses many ounces (in one instance over a quart) of pus have been evacuated.

The cutaneous lesions are found chiefly in the form of irregular, ragged, rather superficial ulcers, and have a soft base, a granulating floor, and a purulent or sanguinopurulent discharge which often forms bulky crusts. Some of the ulcers acquire a fungoid or papillomatous appearance; in others the borders are slightly elevated and contain miliary abscesses. In some instances, as the result of transformation of one of the above-described ulcers, but more commonly as the result of infection of the skin with the secretions from them, there are formed the characteristic lesions of cutaneous blastomycosis. These are elevated patches of various sizes, with a verrucous or irregular papilliform surface, a soft,

pus-infiltrating base, and a purplish-red, sloping border in which, with the aid of a hand-glass magnifying from two to six diameters, the characteristic miliary abscesses can be detected.

The joints or the tissues immediately about them were affected in eleven cases (7, 8, 9, 14, 15, 17, 18, 19, 20, 21 and 22). In some instances the joint showed for weeks no evidence of disease except pain, with or without a small amount of swelling. In others the inflammatory symptoms were more pronounced, and in two cases so marked that a diagnosis of acute articular rheumatism was made. Inflammation and caries

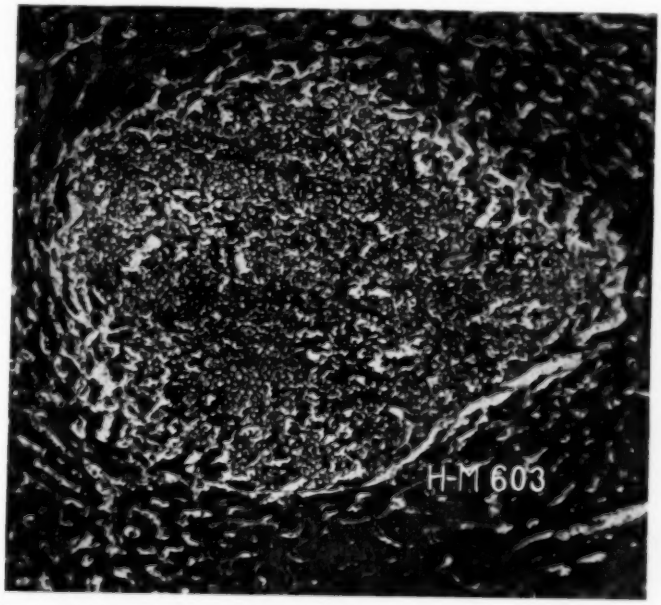


Fig. 9.—Section of liver showing miliary abscess crowded with the organism. (From Case 5.).

of some of the bones were recognized clinically in nine cases (1, 7, 8, 9, 13, 18, 19, 20 and 22). Spondylitis was present in Cases 7, 8 and 18. The eye was involved in two cases; a corneal ulcer in Case 1 and partial loss of vision in one eye in Case 20. From the corneal ulcer, and from the vitreous by aspiration in Case 20, pure cultures of blastomycetes were obtained. Slight or a moderate local or general enlargement of the lymph glands was noted in six cases (1, 4, 5, 7, 14 and 19), but in none was adenopathy at all prominent.

DIAGNOSIS.

The disease in its various manifestations might be confused with an ordinary pyemia, tuberculosis, syphilis, nephritis or articular rheumatism. When abscesses or cutaneous lesions are present it is a simple matter to establish the diagnosis by the examination of pus or tissue. The addition of a 1 to 10 per cent. solution of potassium hydrate to the specimen will make the double-contoured capsule of the organism stand out clearly. When the parasites are present in very small number they can be more easily demonstrated in tissue by allowing fragments to disintegrate in the potassium hydrate solution or more slowly in 50 per cent. alcohol. The organisms, when present, are easily found in the sediment.

In most of the cases in which systemic symptoms preceded the appearance of the abscesses there were indications of pulmonary, gastrointestinal or kidney disease, and in several blastomycetes were demonstrated in the sputum, feces and urine. They are less difficult of demonstration either in secretions or in tissue than tubercle bacilli. In every case of the formation of multiple abscesses with symptoms of a general pyemia, as well as in cases of what appear to be atypical tuberculosis, the possibility of infection with blastomycetes should be considered.

TREATMENT.

The treatment of systemic blastomycosis has been on the whole very unsatisfactory; but it is probable that if the diagnosis can be made early the proper employment of potassium iodid, tonics and hygienic measures, including possibly a change of climate, would give much more favorable results. This statement is based on the fact that nearly all the cases of cutaneous blastomycosis have been improved, and a number have recovered completely, under the influence of potassium iodid. Furthermore, in Gilchrist's case (No. 4 of this series) the nature of the systemic condition was recognized at the very outset, owing to the fact that it had been preceded for several years by local cutaneous lesions, and under the influence of potassium iodid the patient made a prompt recovery. Patients B and C, of the doubtful cases appended to this series, also made good recoveries under this treatment. In Herrick and Garvey's case (No. 13) the patient, while in Chicago, did not improve greatly under the treatment, which included the use of potassium iodid, and her condition was considered hopeless; but on removing to California she made complete recovery. In all the other cases in this series the disease was well advanced and the patient very much reduced in strength and weight before beginning the treatment. The hygienic surroundings were also unfavorable in several instances. In a few of the cases the use of potas-

sium iodid was followed by decided temporary improvement, but in the majority it apparently had no influence. It is probable that, as in some cases of cutaneous blastomycosis, large doses (half an ounce or more daily) may be required to produce any effect. The use of sulphate of copper internally, as suggested by Bevan, is worthy of trial, though it proved of no benefit in two or three cases in which it was used.

Local lesions should be treated like those of cutaneous blastomycosis, with local antiseptics, of which a 1 per cent. solution of sulphate of copper is one of the best, and with the *x*-rays.

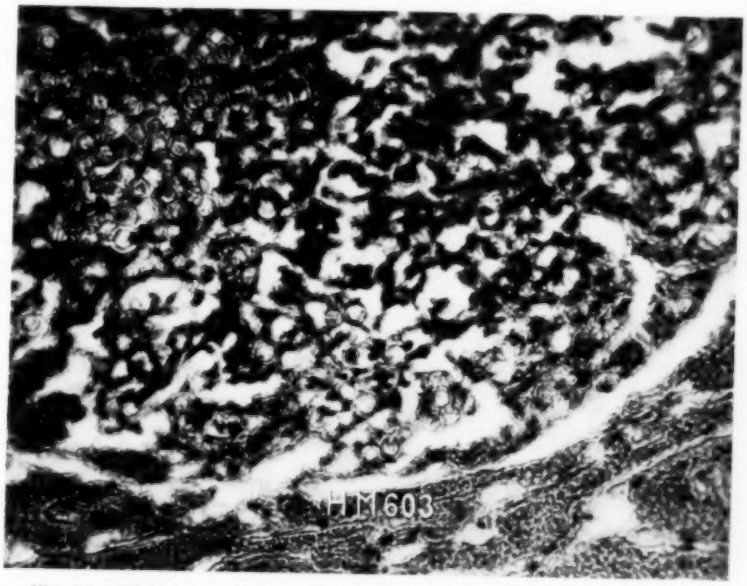


Fig. 10.—Higher magnification of Fig. 9, showing one edge and a part of the abscess (× 350).

PROGNOSIS.

Of the twenty-two patients, two have recovered (4 and 13), seventeen are dead, and three[5] (12, 15 and 17) are failing rapidly and probably can live but a few weeks. The prognosis is evidently exceedingly unfavorable, though, as suggested under the head of treatment, we believe that with an early diagnosis and proper treatment, including good hygienic surroundings, the mortality can be greatly reduced.

5. No recent report has been received regarding the condition of these three patients.

SUMMARY: RELATION OF BLASTOMYCOSIS TO COCCIDIOIDAL GRANULOMA.

A series of eighteen cases have been reported, chiefly from California, by Wernicke, Rixford and Gilchrist, D. W. Montgomery and Morrow, Ophüls and Moffett, and others, under the name of protozoic skin disease or coccidioidal granuloma.[6] A comparative study of the reports of these eighteen cases and the twenty-two cases of blastomycosis shows that the two disorders have many features in common, but with a few more or less essential points of difference.[7]

The following features are common to the two diseases: A chronic infectious process characterized by the formation of multiple abscesses, nodules and miliary tubercles, which involve practically all of the organs and tissues of the body, including the skin, subcutaneous tissue, muscles, bones, joints, internal organs and nerve tissues; symptoms closely simulating miliary tuberculosis or a chronic pyemia; multiformity of cutaneous lesions, which may be primary, but are commonly secondary in origin; a marked tendency to involve joints; progressive emaciation and loss of strength with death usually from gradual exhaustion. In gross pathology and microscopic anatomy they both resemble tuberculosis, but differ from it inasmuch as in both blastomycosis and coccidioidal granuloma the organisms are pyogenic. The two conditions further resemble each other and differ from tuberculosis in the results of animal experiments in which subcutaneous inoculations are ineffective, though intraperitoneal and intravenous inoculations are quite uniformly successful in reproducing the disease. The infection atrium in several cases of both series has apparently been the respiratory tract.

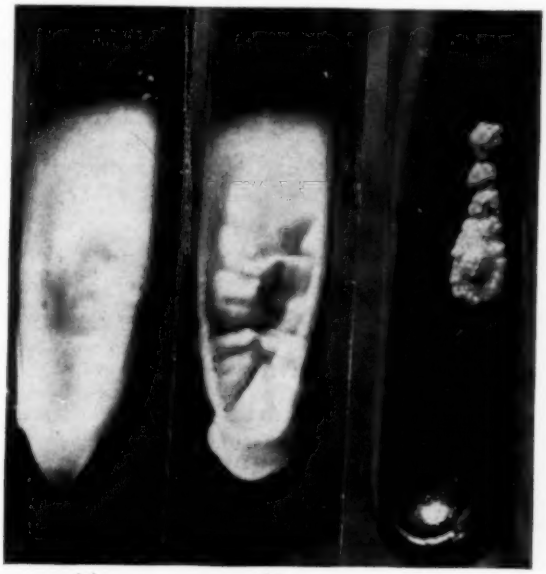
As to points of difference, the average course of the coccidioidal disease appears to be somewhat shorter and there is a much greater tendency to extension through the lymphatic channels than in blastomycosis; these two features being due apparently to the fact that in tissues the organisms of coccidioidal granuloma multiply by endogenous spore formation, while in blastomycosis they proliferate solely by budding. It is true that in Cases 7 and 14 of this series certain cellular

6. Ophüls (Jour. Am. Med. Assn., 1905, xlv, 1291; and King, *Ibid.*, 1907, xlviii, 743) give summaries and reviews of these cases. Both of these men discuss the relation of coccidioidal granuloma to blastomycosis, but both look on the latter chiefly as a local disorder and make the statement that but one case of blastomycosis had become generalized, Ophüls thus overlooking five cases, and King ten cases of systemic blastomycosis, that had been published when they made their reports.

7. Since this paper was read an article has appeared by Hektoen, Jour. Am. Med Assn., 1907, xlix, 1071, in which the relation of the two disorders is ably discussed.

forms suggested strongly endogenous spore formation, but the further development of the spore-like bodies could not be demonstrated. In cultures the organisms of both series grow as mold fungi, showing some slight differences in their gross appearances which may or may not prove to be important. Further study along uniform lines of investigation will be necessary before a satisfactory classification of the organisms in either series will be possible.

Blastomycosis and coccidioidal granuloma are undoubtedly closely related disorders, much more closely related to each other than is either



(a) (b) (c)

Fig. 11.—Cultures four weeks old: (a) On glucose agar; (b) on glycerin agar grown at room temperature; (c) on glucose agar grown in incubator.

to tuberculosis. It may be that further study will remove the one fundamental difference between them, that is, the behavior of the organisms in tissue, and prove the conditions to be but varieties of the same process. Dr. Hyde[8] suggests that the recognized differences between the two disorders may be due wholly to climatic influence. On the other hand, it is probable that there may be several varieties of blastomycetes and other

8. Hyde: Jour. Cutan. Dis., 1907, xxv, 34.

closely related fungi which are capable of producing in man a series of disorders of the same general clinical and pathologic type.

SUMMARY—UNDOUBTED CASES.

CASE 1.—BUSSE AND BUSCHKE:[9] The patient, a delicate woman, aged 31, the wife of a shoemaker, was born and lived in Germany. Since early childhood she had had repeated attacks of glandular swellings in the neck and axillæ. At the time of her examination most of the palpable glands were slightly enlarged.

According to Busse, the disorder under consideration began as a tumor similar to a gumma or softened sarcoma below the knee, though Buschke states that, several months prior to the formation of the tumor, acne-like lesions appeared on the face and neck. These lesions underwent necrosis in the center and formed pea-sized or slightly larger ulcers, some of which healed spontaneously. Later many other similar, and some slightly larger, ulcers appeared. These ulcers were round, with sharply defined, ragged, somewhat undermined, slightly infiltrated wall-like edges, and were surrounded by firm and livid borders. The bases of the ulcers were soft, the floors covered with granulations and tenacious reddish-gray secretions. Subcutaneous nodules also were seen, some of which developed into ulcers. The tumors below the knee formed an abscess which extended to and involved the knee joint. A few months later an abscess formed in the right ulna near the elbow, and another in the left sixth rib. The patient developed bronchitis, with varying temperature and irregular pulse, and died of gradual exhaustion a little more than a year after the appearance of the abscess below the knee.

A double-contoured, yeast-like fungus was obtained in pure culture from the different abscesses, the cutaneous lesions, a corneal ulcer, and the blood. It could not be demonstrated in the urine.

At the necropsy, granulation foci or abscesses were noted also in the lung, left kidney and spleen. Microscopic tubercles in the lungs contained no tubercle bacilli. From all these areas the yeast-like fungus was isolated. The organism developed in cultures by budding, and appears to have corresponded in all essentials to the organisms seen in blastomycosis. An adventitious capsule was described, similar to that recorded in the Curtis case (Case 2). Animal experiments showed the organism to be pathogenic for white mice, guinea-pigs, rabbits and dogs, and demonstrated the absence of tuberculosis in the case.

CASE 2.—CURTIS:[10] The patient was a man, aged 20, who rather rapidly developed multiple tumors on various parts of the trunk, neck, extremities and groin. Some tumors were firm and the skin over them intact; others formed abscesses which broke and discharged. The tumors were myxomatous in character, and many were composed almost entirely of double-contoured and budding organisms, both intracellular and extracellular. In about a year the patient died from meningitis of undetermined nature.

Cultures of the organism were obtained, and in the hands of Anna Stecksen animal experiments were successful, inoculations in white rats producing miliary tumors in the pleura, spleen, kidneys and lungs, from which the organism was recovered.

9. Busse: Centralbl. f. Bakteriol. u. Parasitenk., 1894, xvi, 175; Virchow's Arch. f. path. Anat., 1896, cxlvi; Die Hefen als Krankheitserreger, Berlin, 1897. Buschke: Volkmann's Samml. klin. Vortr. (Chir.) 1898, No. 218; Die Blastomykose, Bibliotheca medica, Abt. Dermat. Stuttgart, 1902.

10. Curtis: Ann. de l'Inst. Pasteur, 1896, x, 449.

CASE 3.—MONTGOMERY AND WALKER:[11] The patient, an unusually well-developed, vigorous man, 33 years old, a carpenter, and resident of Chicago, came under observation in August, 1894, for a cutaneous disorder on his back. This began seven years before as a pimple, on the site of an infected scratch, and had developed to form a large, irregular, elevated, verrucous patch, which, for want of a better diagnosis, was considered a very unusual form of verrucous tuberculosis. The man's general health had been unaffected.

Two months later (October, 1894) he presented a sensitive point on the ulna near the elbow, the entire joint being very much swollen and red. These symptoms disappeared in a few days. A week later he had a severe chill, followed by five days of high temperature and great depression accompanied by the appearance, just below the left scapula, of two deep-seated, globular, dull-red swellings, one-half inch and one inch in diameter. They suggested the tumors sometimes seen in erythema nodosum. One lesion healed, leaving a pigmented area; the other gradually assumed the characteristics of the original cutaneous lesion.

During the next six months the patient had seven or eight similar attacks, accompanied by the appearance of subcutaneous and cutaneous lesions on the back and face. During this time his general health deteriorated greatly. In March, 1895, he entered the county hospital. No definite systemic disorder could

Fig. 12.—Sediment from tissue disintegrated in 50 per cent. alcohol showing organisms in various stages of budding.

be detected at this time. Some of the lesions were curetted and cauterized. Two weeks later symptoms of pulmonary disease were recognized. A few days before his death, forty-three days after the operation, a clinical diagnosis of acute, miliary tuberculosis was made.

At the autopsy the lungs, liver, spleen and kidneys were found to be studded with miliary bodies, and the diagnosis of miliary tuberculosis was accepted. Five years later, however, histologic study of the infiltrated areas of the lungs showed the typical structure of the blastomycotic nodule, including large numbers of budding organisms. Sections from the cutaneous lesions had shown the characteristic infiltration of cutaneous blastomycosis, with giant cells, miliary abscesses, epithelial hypertrophy and budding organisms.

Cultures were not made. Several guinea-pigs inoculated at different times with tissue from the cutaneous lesions, and at the time of the autopsy with tissue

11. Montgomery, F. H.: Jour. Cutan. Dis., 1901, xix, 318. Walker and Montgomery: Jour. Am. Med. Assn., April 5, 1902.

from the deep-seated organs, developed no tuberculosis. Prolonged search over several hundred sections disclosed no tubercle bacilli, except possibly four or five which morphologically and in staining qualities appeared to be identical with tubercle bacilli, but were found in a small abscess opening on the surface of the skin, where secondary infection could easily have occurred.

CASE 4.—GILCHRIST:[12] The patient was a negro, 28 years old, and acquired the disease while serving a sentence in the penitentiary. In July, 1907, he noticed a pimple or small boil on the abdomen and a month later a similar lesion appeared in the right loin. Both gradually increased in size and spread to form superficial ulcers. These were not painful but never showed any tendency to heal.

About four years later subcutaneous swellings appeared simultaneously in the right groin and right breast. These were painful, became swollen, and ruptured in three or four weeks, discharging a thin mucoid pus. About two weeks later an egg-sized, soft swelling appeared at the lower end of the spine, and a small, soft swelling occurred in the axilla.

At this time the patient was in apparently good general health, aside from a systolic heart murmur and irregular temperature varying from 99 to 101.5. There was some adenopathy in the axillæ and in the groins. Of the original ulcers, one, about 9 by 16 cm., occupied the right half of the abdomen, and another, about 8 by 14 cm., extended from near the right border of the first over the lumbar region to the back. Both showed the characteristic borders, with miliary abscesses and other features of cutaneous blastomycosis. The man recovered in about six weeks under treatment with iodid of potassium.

Pure cultures of blastomycetes were obtained from an unbroken abscess in the back and from other lesions. None could be obtained from the blood. A dog inoculated with pus from an unbroken abscess developed characteristic nodules in the lungs.

CASE 5.—ORMSBY AND MILLER:[13] The patient, aged 56, was a Swede, resident of Chicago, and a machinist by occupation. For several years he had lived over a stable. He was never robust, and for ten years had been rather feeble. In April, 1902, he caught cold which settled in his chest; he coughed considerably, had scanty expectoration streaked with blood, and became so weak he was forced to stop work. In July and August he had lesions on the nose and thigh, which healed under treatment.

In September he entered the hospital, badly emaciated, complaining of a severe and persistent pain in the back. Physical examination disclosed no cardiac or pulmonary disease; blood examination showed anemia; urine was normal.

In October, when the case came under the observation of Drs. Hyde, Ormsby and Miller, subcutaneous nodules which softened, ruptured and formed ulcers, had appeared on the right arm and both legs. From this time successive crops of similar lesions appeared at short intervals on different parts of the trunk, face and limbs, as many as ninety-three being present at one time; while at death the entire surface of the body was covered with lesions in varying stages of development and involution. They appeared first as pea-sized or larger nodules, set deep in the hypoderm, and could be detected only by palpation. As they increased in size, approached the surface, and softened, the color of the skin passed through varying shades of dark red, blue, and even black. The abscesses thus formed eventually ruptured, discharged, and formed unhealthy-

12. Gilchrist: Brit. Med. Jour., 1902, ii, 1321.

13. Ormsby, O. S., and Miller, H. M.: Systemic Blastomycosis, Jour, Cutan. Dis., 1903, xxi, 121. Otis, F. J., and Evans, Newton: Morphology and Biology of the Parasite from a Case of Systemic Blastomycosis, Jour. Am. Med. Assn., 1903, xli, 1074. This is a bacteriologic report on the case of Ormsby and Miller.

looking ulcers of various sizes. The majority of these ulcers had rough, irregular edges, necrotic floors, soft bases, and a purulent and hemorrhagic discharge, which often dried to form heavy crusts. Only one of these ulcers assumed the characteristics of cutaneous blastomycosis. The patient's general health deteriorated rapidly, his temperature ranging from 100 to 103, his pulse being rapid and feeble. A month after entering the hospital bronchial breathing and other signs of pulmonary involvement were present and gradually grew more pronounced. There was moderate general adenopathy and slight edema of the legs. Toward the end the patient became drowsy and at times comatose. He died December 4, about eight months after the beginning of his disease.

The autopsy showed characteristic blastomycotic nodules and extensive infiltration in the lungs, which were almost entirely destroyed, and in the spleen. The kidneys, pancreas, larynx and trachea showed the same type of lesions, but

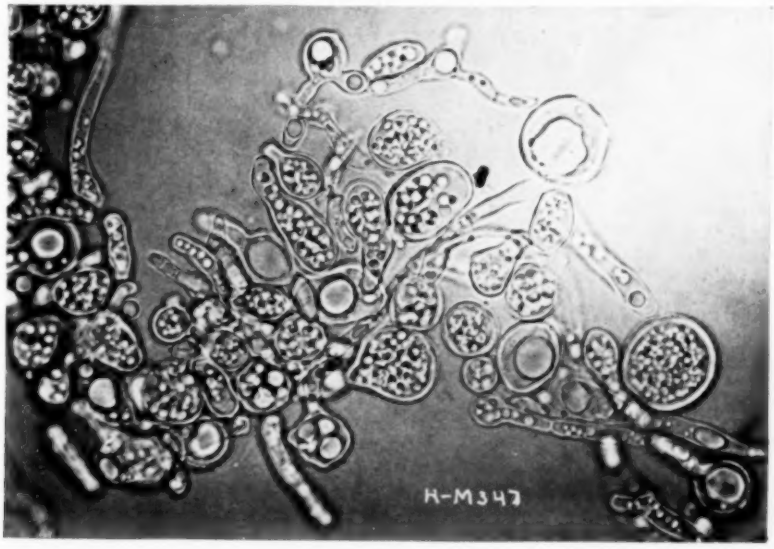


Fig. 13.—Old culture showing large round bodies and short thick mycelium containing spore-like bodies.

in small numbers. The histologic examination showed the structure characteristic of blastomycosis, and the parasites which were present in immense numbers. Portions of the lung tissue seemed to have been almost wholly replaced by the parasites. Amyloid degeneration was present in the kidneys. A small, deep-seated subcutaneous nodule showed on section practically no change in the overlying epidermis, with only slight changes in the corium proper, consisting of vascular dilatation, some perivascular infiltration, edema, slight degeneration of the collagen, and in places a small amount of cell infiltration. The infiltration was limited almost entirely to the subcutaneous tissue and occurred chiefly in the form of fairly well-defined zones. The characteristic structure

consisted of a collection of the organisms, of leucocytes, especially polymorphonuclear, and red blood-cells, around which were seen giant cells, connective-tissue and plasma cells. In places the component parts of the infiltration were more or less intermingled.

Pure cultures of the organisms were obtained repeatedly from cutaneous and subcutaneous lesions, and after the patient's death, from the liver, spleen and kidneys, and from beneath the pleura. Inoculated guinea-pigs developed local lesions, and one pig developed characteristic nodules in the liver and spleen from which the organism was recovered. One of the physicians attending the autopsy was accidentally inoculated on his finger, on which there appeared later a lesion characteristic of cutaneous blastomycosis.

Tuberculosis as a complication was absolutely excluded by the failure, after careful search, to find tubercle bacilli either in the sputum or in any of the tissues of the patient; by the failure of the patient to react to the tuberculin test, and by the fact that, of the ten guinea-pigs and two rabbits inoculated with tissue from the patient, none developed any symptoms of tuberculosis.

CASE 6.—CLEARY:[14] The patient, a man, aged 23, Italian, resident of this country three years, entered the county hospital in May, 1903, giving a history of a cold and diarrhea of several months' duration. He had a severe cough with mucopurulent expectoration, had lost twenty-five pounds, and was extremely weak.

Examination showed, immediately above the right sternoclavicular articulation, an opening to a sinus from which a small amount of pus escaped. The physical signs were suggestive of disease of the apex of the right lung, but the respirations were normal and no tubercle bacilli could be demonstrated in the sputum. The spleen was palpable, the feet and legs were slightly edematous. The urine showed constantly marked albuminuria with abundant hyaline and granular casts. The temperature remained subnormal, the pulse rapid and weak, and the patient died nine days after entering the hospital. The clinical diagnosis was nephritis.

The autopsy showed no cutaneous or subcutaneous lesions except the sinus in the neck, which communicated with a small abscess. Numerous pin-head to pea-sized gray or yellow nodules with softened, usually necrotic, centers from which whitish pus could be expressed, were found abundantly in the lungs, and in smaller numbers and of smaller size in the kidneys, adrenals and liver. Microscopic lesions were found also in the myocardium and spleen. There was a chronic parenchymatous nephritis, atrophy of the heart, fibrous obliterative pleuritis, laryngitis, tracheitis and bronchitis. The histologic structure of the nodules was characteristic of blastomycosis, including the presence of budding organisms. The spleen, kidney and adrenal showed marked evidence of amyloid disease. The cause of death was evidently a generalized infection with blastomycosis and a rather extensive amyloid disease. No cultures were taken.

CASE 7.—EISENDRATH AND ORMSBY:[15] The patient, a Polish laborer, 33 years old, stated that his present disease began February, 1904, with a feeling of discomfort in the right side of the chest. About four months later cutaneous lesions appeared below the left ankle and gradually increased in size. These were followed at short intervals by other lesions on the cheeks, forearms, face, chin and neck. In November he developed great muscular weakness and marked swelling of the feet and ankles.

14. Cleary: Medicine, November, 1904.

15. Eisendrath, D. N., and Ormsby, O. S.: Systemic Blastomycosis, Jour. Am. Med. Assn., 1905, xlv, 1045. Le Count, E. R., and Meyers J.: Systemic Blastomycosis, Jour. Infect. Dis., 1907, iv, 187. This is an account of the termination and postmortem findings in the case of Eisendrath and Ormsby.

On admission to the hospital, in February, 1905, he was very much emaciated, anemic, and exceedingly weak; with moderate temperature, marked edema of the face and extremities, clubbed nails, some inguinal adenopathy, bronchial breathing, dullness over the right upper lobe, absence of lung expansion, and other slight evidences of more extensive involvement of the lungs. The urine contained albumin and casts; budding blastomycetes were demonstrated in the sputum (the first case in which the demonstration was made); there were a number of subcutaneous nodules and superficial ulcers with but little induration and considerable sanguinopurulent discharge. The edges of the ulcers were slightly elevated and surrounded by a bluish-red halo in which were a few miliary abscesses. Some of the lesions were more or less papillomatous. After four months of treatment with potassium iodid internally, and with radiotherapy, antiseptic dressings, and surgical interference locally, the man improved greatly. After leaving the hospital and neglecting treatment, he became worse and returned to the hospital in September with all symptoms exaggerated and with a dorsal spondylitis. Further developments included: ankylosis of both knees, which, with the left

Fig. 14.—Section of a characteristic nodule from the diaphagm of a guinea-pig. (From Case 14.).

elbow, were enlarged and tender, but showed no redness or elevation of temperature; edema; moderate general adenopathy; a diarrhea with mucopurulent discharge, blood, and budding blastomycetes in the feces. There was slight leucocytosis; temperature varied from normal to 103. The patient died in a convulsion August, 1906, two and one-half years after the beginning of the disorder.

The autopsy showed: "Blastomycotic bronchopneumonia; blastomycosis of the peribronchial lymph nodes, of the pleura, the subpleural, and retropharyngeal tissue, the liver, the kidneys, the colon, the spinal column (dorsal vertebræ), the external spinal dura, the cerebellum, the left elbow, both knee and ankle joints, and of the skin and subcutaneous tissues with ulcerations, fistula, and scars; fibrous induration at root of right lung; fibrous pleuritis; passive hyper-

emia of liver and spleen; serous atrophy of adipose tissue; emaciation, adenoma of thyroid and accessory spleen." Characteristic lesions were discovered in the cerebrum after the report of the case was published.

Histologic examination demonstrated the typical nodules of granulomatous tissue with necrotic centers, giant cells, and budding organisms in the lungs, peribronchial lymph glands, pleura, and kidneys. Le Count and Meyers believe that in the cerebellum they found an area in which the organisms multiplied by endosporulation. They did not, however, demonstrate the intermediate stages of development between the supposed spores and mature organisms.

Blastomycetes were demonstrated in the sputum and in pus, and were obtained in pure culture from subcutaneous abscesses.

No tubercle bacilli could be found in pus, sputum or tissue, and guinea-pigs inoculated with pus and tissue did not develop tuberculosis.

CASE 8.—BASSOE:[16] The patient, a boy, aged 17, a native of Chicago, entered the service of Dr. Senn at the Presbyterian Hospital, July 26, 1904. Four months prior to this date he slipped and fell, injuring the right shoulder, which became painful and swollen. For some time previous to this accident he had pain through the lumbar region and a "gnawing" sensation in the upper part of the right lung. He had a cough, low fever, night sweats, and had lost thirty pounds in weight. The urine was normal. July 26, from a large abscess over the right scapula an ounce of slightly bloody pus was removed with a trocar. August 9, a large abscess in the right lumbar region was incised and a pint of pus evacuated. During the following two months a daily rise in temperature to 100 and 101 was noted. On September 1, a blood count showed 4,180,000 erythrocytes, and 19,500 leucocytes. On November 15, the patient left the hospital improved, but was readmitted on Decemer 18. The abscesses had refilled; temperature varied from 102 to 103; nausea, vomiting, and diarrhea were present at times. Blood count in January showed marked anemia, hemoglobin 50 per cent. In May, the urine showed large quantities of albumin with casts. During the last two months of the patient's life, diarrhea was constant. The limbs became edematous and painful. There was also considerable pain in the abdomen; irregular fever persisted, and emaciation increased. The patient died June 27, 1905, approximately fifteen months after the apparent beginning of the disease.

The autopsy and histologic examination showed: Chronic subcutaneous blastomycotic abscesses in right scapular region and in loin, abscess and sinus walls made up of vascular granulation tissue rich in polymorphonuclear leucocytes, mast cells, and blastomycetes; blastomycotic caries of fourth and fifth lumbar vertebræ, with bilateral psoas abscesses; disseminated blastomycotic bronchopneumonic foci in both lungs; areas of necrosis with Langhans' giant cells in the mediastinal glands; amyloid degeneration of spleen, liver, adrenals, retroperitoneal, mesenteric and mediastinal lymph nodes, kidneys and colon; bilateral fibrinous pleuritis, and mild serofibrinous peritonitis; chronic parenchymatous nephritis; atrophy of the heart; pulmonary edema; edema of feet and thighs; tigrolysis of ganglion cells of cerebral cortex and ventral horns of cord (only cervical portions of latter examined). The stiking features were the extensive amyloid degeneration, and the large number of lesions containing organisms in the bones.

Blastomycetes were found repeatedly in pus from the various subcutaneous abscesses and in the sputum, but could not be demonstrated in the feces. Cultures were obtained; inoculated animals developed blastomycotic lesions. Details were not given in the report. Tubercle bacilli could not be found in pus, sputum or tissue, and inoculated guinea-pigs did not develop tuberculosis.

16. Bassoe: Jour. Infect. Dis., 1906, iii, 91.

CASE 9.—IRONS AND GRAHAM:[17] The patient, a German, 47 years old, had worked for a number of years in a Chicago lumber yard. In March, 1905, a small subcutaneous nodule appeared on the inner surface of the right thigh, increased to the size of a small hen's egg, softened, broke, discharged a bloody pus, and slowly healed, leaving an indurated reddish-brown scar. Other similar lesions appeared in rapid succession on the legs, hips, arms and face. Later, lesions appeared over the ankles, which became swollen, red and tender, interfering greatly with walking. Systemic symptoms were limited to a slight fever and to gradually increasing weakness.

On September 11, when admitted to the Presbyterian Hospital, he was weak and anemic, but examination detected no diseases of the thorax or abdomen. Scars, partially healed ulcers, subcutaneous nodes and abscesses were present on the forehead and limbs. The superficial lesions began as small, hard, subcutaneous nodes, which gradually softened, broke through the skin, and discharged bloody pus in which were a large number of blastomycetes. Other abscesses were

Fig. 15.—Giant cell containing a budding organism from the nodule shown in Fig. 14. (From Case 14.).

larger and deeper, some of them being subperiosteal in origin. There was a tendency in the deeper lesions to extensive dissection along the intermuscular fascia. Abscesses which had ruptured spontaneously formed ulcers, having irregular, granulating floors, and rather ragged, slightly raised edges in which an occasional miliary abscess could be seen, such as are common in the lesions of cutaneous blastomycosis. The ulcers were surrounded by dull red or purplish zones and were often covered by dry, hard crusts. Resulting scars were usually slight in comparison with the extent of the preceding ulcers. Abscesses which were incised and evacuated early healed without formation of the above described ulcers. After a short period of improvement the patient developed pain in the

17. Irons, E. E., and Graham, E. A.: Generalized Blastomycosis, Jour. Infect. Dis., 1906, iii, 666.

chest, cough with mucopurulent expectoration often streaked with blood, and physical signs indicating consolidation of the upper portions of both lungs. The patient grew steadily weaker, new lesions appeared over the body, and toward the end there was marked destruction of subcutaneous tissue with consequent undermining of the skin, and at several points bone was completely denuded. Temperature varied from normal to 102. The patient had constant leucocytosis varying from 12,500 to 21,200. The urine showed slight albuminuria with occasional casts. The patient died Jan. 18, 1906, ten months after the appearance of the first lesions.

The autopsy showed: "Miliary blastomycosis of lungs and spleen; ulcerative blastomycosis of the upper lobe of the left lung; multiple subcutaneous abscesses and sinuses involving the face, scalp, and all the extremities; retroesophageal abscess with erosion of the bodies of the seventh cervical to the fifth dorsal vertebræ (inclusive), and of the anterior surfaces of the vertical extremities of the second to the fifth left ribs; erosion of left parietal bone; deep sloughing ulcer of the right thigh; abscess of thyroid cartilage; subpleural hemorrhages of right lung; bilateral fibrous pleuritis; hyperplastic splenitis; hyperplasia of mesenteric lymph glands; brown atrophy of the heart; colloid goiter (all lobes); slight sclerosis of anterior mitral leaflet and root of aorta; chronic gastritis; localized fibrous peritonitis; chylous ascites (slight); slight atrophy of liver; retention cysts of left kidney."

Histologic examination of lung tissue showed characteristic nodules with necrotic centers containing organisms in large numbers. Serial sections proved the disease to be a bronchopneumonia. Two blastomycetes were seen in a large blood vessel. From the retroesophageal abscess giant cells containing blastomycetes and other cells peculiar to this granuloma were demonstrated. The spleen showed areas of necrotic tissue with blastomycetes but no giant cells. Colloid changes were present in the thyroid.

Cultures of the organism were obtained from the subcutaneous abscesses, sputum and kidneys (though smears and sections made from the kidney did not show the organism). No cultures could be obtained from the blood or from the urine. General miliary blastomycosis was produced in one rabbit by inoculation of a pure culture. At the autopsy the *Streptococcus pyogenes* was obtained in pure culture from the cerebrospinal fluid, liver, spleen and kidney; the *Staphylococcus pyogenes aureus* was found in the liver and spleen, and in pus from the retroesophageal and knee abscesses.

Tubercle bacilli could not be found in the sputum, pus or tissue, and guinea-pigs inoculated with pus and tissue did not develop tuberculosis.

CASE 10.—HEKTOEN AND CHRISTENSEN:[18] The patient was an Iowa farmer, aged 28. In November, 1904, he was attacked with an acute fever lasting one week, during which he suffered with headache, chills, and pains in the back and limbs. At the end of the second week numerous spots and lumps appeared on the face, head, neck, hands, forearms, limbs and back. Some of these subsided, while others enlarged and formed indolent ulcers. Several of these healed leaving atrophic scars. In June, 1905, some of the lesions increased in size; and submaxillary, supraclavicular, and other abscesses formed. In December, after a period of improvement, all the lesions became much worse.

On admission to the hospital, Jan. 10, 1906, there were in all sixty lesions of the skin and subcutaneous tissues. There was loss of weight and some pulmonary symptoms. The patient left the hospital April 6, somewhat improved. We are informed by Dr. Hektoen that on the patient's returning home new lesions

18. Christensen, C., and Hektoen, L.: Generalized Blastomycosis, Jour. Am. Med. Assn., 1906, xlvii, 247. (Two cases.)

continued to appear, and that the patient died three or four months later of a sudden paralysis. There was no autopsy.

Blastomycetes were obtained in pure culture from the abscesses and were demonstrated in sections taken from the ulcers. Neither blastomycetes nor tubercle bacilli could be demonstrated in the urine or sputum.

CASE 11.—HEKTOEN AND CHRISTENSEN: Recorded with Case 10. The patient was a Norwegian farmer, 58 years old, living in Iowa. There was a marked tuberculous history in the family. The patient had been a dipsomaniac for many years, but always healthy. In January, 1905, he was taken with an acute illness and three weeks later a large abscess formed in the left lumbodorsal region. Later there was another attack with chills and general debility, followed in a short time by swelling under the skin on the left forearm. In May, red spots, 2 cm. in diameter and suggesting ringworm appeared over the right thigh and forearm. These grew to form elevated, granulated areas, became crusted, and had an offensive odor. Some of the ulcers partially healed, but soon formed again. In October,

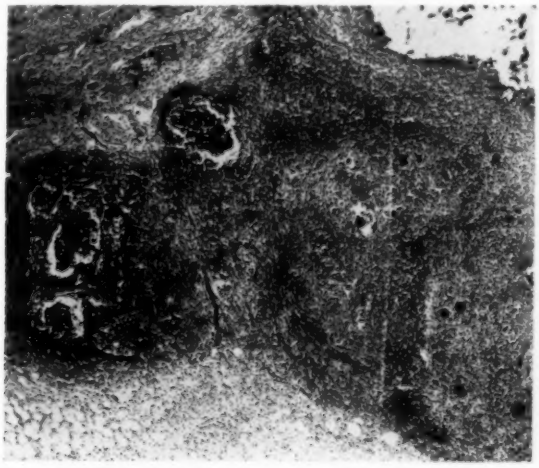


Fig. 16.—Section from testicle of a guinea-pig showing characteristic abscesses and giant cells. (From Case 14.).

painful abscesses appeared on the right arm above the elbow and on the left forearm. There was no adenopathy. There was slight temperature with bronchial râles. We are informed by Dr. Hektoen that death occurred in the early part of 1907.

Histologic examination of the ulcers showed the characteristic structure of blastomycosis and the organisms. Blastomycetes were demonstrated in pus and obtained in pure culture. Early examination of the sputum was negative, but later it was found to contain tubercle bacilli but no blastomycetes.

CASE 12.—COLEY AND TRACEY:[19] The patient, a New York policeman, 27 years old, cut his left foot on a clam-shell in August, 1906, producing a slight

19. Coley, W. B., and Tracy, H.: Case of Oidiomycosis, Jour. Med. Research, 1907, xvi, 237.

wound, which healed readily. The following December he had severe pain in the lumbar region and a few days later on the dorsum of the left foot, where a swelling appeared, softened, and discharged through a sinus between the great

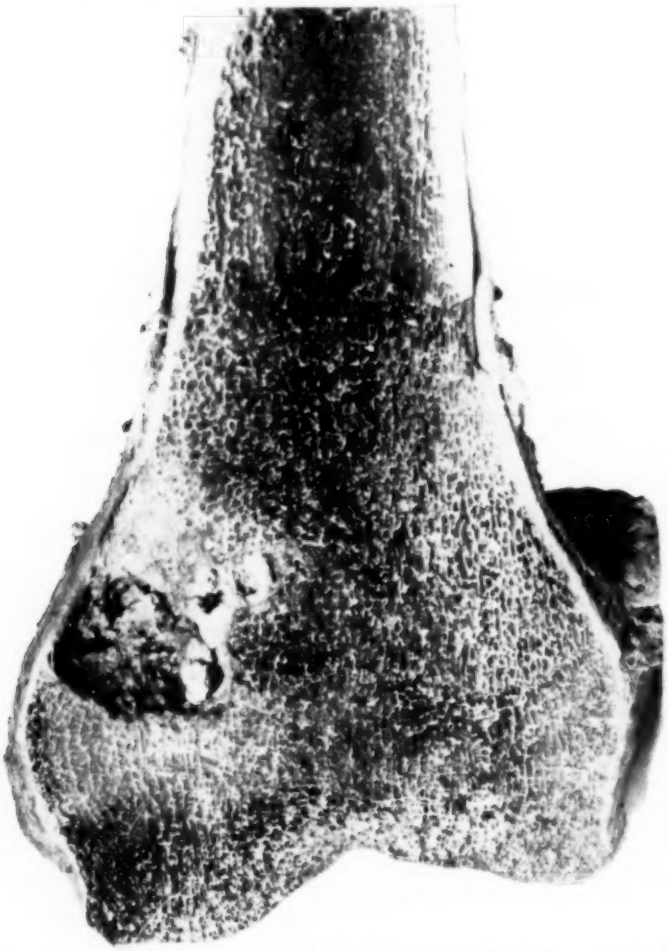


Fig. 17.—A blastomycotic abscess in the lower end of the femur. The light or infected area has the appearance of an infaret. (Courtesy of Dr. A. M. Stober.)

and second toes. The skin over the swelling, though tense, was not red. A week later, similar lesions appeared on the dorsum of the right foot and thigh. Above the knee two small, papillomatous, crust-covered tumors appeared in the

skin. Many other subcutaneous swellings, varying from the size of a hazel-nut to that of a small egg, appeared on various parts of the body, chiefly on the face, arms and thighs. These tumors softened and discharged, forming ulcers or elevated, crust-covered, cutaneous lesions. With the tumors appeared a cough, which persisted and was accompanied by emaciation and loss of sixty pounds in three weeks. The man made no improvement under treatment with potassium iodid but continued to fail in general health. On April 8 he had sixty-five tumors distributed over the various parts of the body. On April 25, many more had developed and the patient was failing so rapidly that it was thought he could not live more than one or two weeks.

Histologic examinations showed granulomatous tissue with giant cells, and double-contoured and budding organisms. Blastomycetes were demonstrated in pus, sputum and tissue, and in the mucopurulent discharge from the rectum. Pure cultures were obtained. A mouse and dog were inoculated successfully.[20]

CASE 13.—HERRICK AND GARVEY:[21] The patient, a married woman, 24 years old, resident of Chicago, was in good health aside from certain neurotic and hysterical tendencies.

The present disorder began April 24, 1904, with "spots like hives and pains like rheumatism" over the left gluteal region. During the two years through which the disorder persisted there appeared seventy-nine different lesions, varying in size from 1 cm. to 8 cm. or more in diameter. They began as slightly reddish or purplish spots accompanied at times with an infiltration below the skin. They gradually became larger, tender, and formed abscesses which would break through the skin and discharge a thick, yellowish pus. A few underwent spontaneous resolution without rupture. Evacuation of the pus left an indolent, granulating ulcer. Extensive undermining of the skin with burrowing of pus occurred in places, especially over the left gluteal region, where, from a large abscess which apparently had its origin in the pelvis, a quart of pus was removed. In some of the lesions bone was destroyed. The scars were comparatively slight and somewhat resembled those of syphilis. The general health gradually became impaired after the first few weeks. There was a slightly elevated temperature, reaching at times 103, together with rapid pulse, hemic murmur, cough, and at times evidences of slight consolidation of the right apex; occasional traces of albumin; loss of weight; low hemoglobin and increase in leucocytes. The patient was neurotic and hysterical, slept poorly, and complained greatly of pain at times. She was treated with large doses of iodid of potassium, tonics, sedatives, and antiseptic local dressings. In February, 1906, she went to California but slightly improved. She lived largely out of doors and gained rapidly. In August, 1906, the last sore disappeared, and July, 1907, she was apparently in perfect health.

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20. Although the organisms in this case multipled in tissue and pus solely by budding and never by endogenous spore-formation, Coley and Tracy class it with cases of coccidioidal granuloma because it was generalized, and make the statement (evidently taken from Ophüls and Brown) that only one case of blastomycosis had become generalized. At the date of their report, eleven cases (with seven autopsies) of generalized systemic blastomycosis had been published in which the clinical histories and the organisms described corresponded closely with those of his own case.

21. Herrick, James B.: Generalized Blastomycosis, Jour. Am. Med. Assn., 1907, xlix, 328. This is a preliminary report; a more complete one is in preparation by Dr. A. C. Garvey. Dr. Hyde, to whom the patient was referred for diagnosis and who saw her after her remarkable recovery, has commented on the influence of climate on the disease; (Jour. Cutan. Dis., 1907, xxv, 34).

Blastomycetes were repeatedly demonstrated in pus from the subcutaneous lesions, from some of which Dr. Ormsby obtained pure cultures.

CASE 14.—MONTGOMERY:[22] The patient was a locomotive engineer, aged 32, in fair general health. In 1902 and 1903, while running a locomotive through a swampy region in the south, he had several attacks, from which he made a more or less complete recovery, of what was considered to be malaria. From January to April, 1903, he was unable to work, being weak and depressed, and suffered from pain in the chest which interfered with his taking a deep breath. He spent the summer in the north and apparently recovered, returning to the south in September. In November, a pea-sized lump appeared beneath the skin on the right cheek. This increased slowly to the size of a hazel-nut, became sensitive and inflamed, and in about four weeks, broke and discharged like a boil. The resulting ulcer never healed but slowly extended peripherally. At irregular intervals during the following eight months, lesions appeared on the lower part of the cheek, on the right jaw, back of the right ear, and under the chin. These all began as small lumps freely movable beneath the skin, and in from two to six weeks formed painful abscesses, which ruptured, forming open ulcers, or masses of infiltration with fistulous tracts leading from them. About two months after the appearance of the first abscess the patient had an attack of dropsy which lasted about ten days. At this time there was detected in the sigmoid region a peculiar hard mass, for which, during the succeeding three months, the patient received a number of injections of Alexander's cancer serum. During this treatment he lost rapidly in weight, but after its suspension largely recovered his general health.

On examination Aug. 9, 1904, he presented the appearance of a man in fairly good general health except that he was under weight, had slight emphysema around the borders of the lung, slight enlargement of the cervical glands, and a peculiar firm mass, apparently due largely to muscular resistance, in the sigmoid area. On the right cheek were two irregularly oval ulcers which showed the characteristic elevated, sloping, dull-red border containing miliary abscesses, a soft, pus-infiltrated base, and a papillomatous surface. Two pea-sized nodules near the border of the larger ulcer were due evidently to inoculation of the skin from secretion from the ulcer. A similar ulcer was located back of the right ear. Smaller ulcers with fistulous tracts leading to deep-seated masses of infiltration were located under the right jaw and under the chin.

The patient was given tonics and large doses of potassium iodid, and the cutaneous lesions were treated with antiseptics and *x*-rays. Under this treatment the man made some improvement but the disease was never completely arrested. In January, 1905, he became weak, emaciated, and cachectic, with irregular temperature and night sweats. A general examination by Dr. Joseph Capps disclosed slight dullness of the apex of the right lung, some enlargement of the spleen, and a leucocytosis of 20,400. The hard mass in the sigmoid area persisted, there were subcutaneous nodules near the symphysis pubis, and bands of infiltrated tissue along Poupart's ligament, most marked in the left side. The thighs could not be fully extended.

In January, new subcutaneous swellings appeared in the neck, breast, groin, foot and elbow. The larger joints were painful but showed no evidence of inflammation. The patient had an irregular temperature varying from 100 to 102. He developed no new pulmonary or other symptoms, but gradually became weaker and died Aug. 29, 1905.

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22. Montgomery: Jour. Cutan. Dis., 1907, xxv, 393. This case was demonstrated before the Chicago Dermatological Society in April, 1905, at which time but four other cases had been reported.

The autopsy made by Dr. Peter Bassoe, showed multiple subcutaneous abscesses with formation of fistulous tracts; a large psoas abscess extending into the thigh and connecting through a fistula with an ulcer in the left groin; localized adhesive peritonitis (chiefly periappendicitis and perihepatitis); and chronic cervical and inguinal lymphadenitis. Only opening of the abdominal cavity was permitted.

Histologic examination showed the characteristic blastomycotic structure, with organisms, in the lungs, spleen, appendix and inguinal lymph glands.

Pure cultures were readily and repeatedly obtained from different abscesses. Nearly every tube inoculated with pus from an unbroken abscess produced a pure culture of blastomycetes, yet smears of pus from these same abscesses showed very few of the organisms of the usual sizes and forms. The organism was unusually pathogenic for guinea-pigs, injection of a pure culture into the abdominal cavity being in each instance followed by extensive systemic infection with the formation of characteristic nodules in many of the organs. From these organs the parasite was obtained readily in pure culture, but was found in exceedingly small numbers, in the usual forms, either in smears or in sections. The number of organisms thus demonstrable seemed to be wholly insufficient to account for the readiness with which cultures were obtained, or for the unusual pathogenicity of the organism for guinea-pigs. Pus from the abscesses and sections of tissue, both from the patient and from inoculated guinea-pigs, however, showed large numbers and masses of round cells, each about the size of a red blood corpuscle, which bore a strong resemblance to small blastomycetes; though the double-contoured capsule and other definite structure were not demonstrable. The large number of these cells, their grouping, and their uniform size suggested multiplication by sporulation, but no relation between them and the larger budding forms could be determined, nor could large bodies containing spores be found. The unusual activity and virulence of this organism could be readily explained by the supposition that in this case the parasite existed abundantly in pus and tissue in small form (the result probably of sporulation), with occasional larger and budding bodies.

CASE 15.—ORMSBY (previously unreported case): The patient was an Indiana farmer, aged 38. In January, 1902, he had suppurative tonsillitis lasting thirty-six days and terminating in pneumonia, which confined him to his bed for seven weeks, following which he had cough with moderate expectoration. Beginning April 25, he was confined to the house eight weeks with a painful swelling in the left knee joint. Another swelling which appeared above and behind the knee was opened and pus removed. Small crusted lesions, which, when opened, gave exit to dark bloody pus, formed on the dorsum of the foot, the right hip, the back of the right hand, and the face. At the time of his examination, July 31, 1903, the patient was pale, anemic, had lost much weight, and was very feeble. There were a number of cutaneous and subcutaneous lesions distributed over the body beside those described above. The cutaneous lesions all began as deep-seated swellings which gradually increased in size, softened, and discharged pus. After several months' treatment with potassium iodid, and radiotherapy, the patient showed some improvement and returned to his home in Indiana. The last report received from the patient's family physician was in May, 1904, twenty-five months after the beginning of his disorder, at which time the man was not expected to live more than a few weeks.

A slightly unusual feature in this case is the fact that practically all the cutaneous lesions, instead of, as in most instances, only a few of them, sooner or later assumed the characteristic features of cutaneous blastomycosis.

Blastomycetes were demonstrated in the pus and secured in pure culture.

CASE 16.—IRONS, E. E. (previously unreported case): The patient, a man, 20 years old, entered the Presbyterian Hospital, Nov. 8, 1905. The preceding January, pains appeared in the left arm and shoulder and, soon after, in the right leg. A small area of tenderness developed two inches below the knee. There was no redness or tumefaction at first, but in a month swelling appeared and gradually extended until it occupied the entire popliteal region at the time the patient entered the hospital. There were also small swellings on the back and in the right lumbar region, and a large one, two inches in diameter, in the left interscapular space. There was no discoloration or pain connected with the lesions.

On the patient's admission to the hospital, physical examination disclosed nothing further than a few signs suggestive of pulmonary disease. There was no cough or expectoration and the patient's general health was only slightly impaired. The abscess in the popliteal region ruptured and discharged a pint of bloody pus. On enlarging the opening and curetting the abscess, a sinus was discovered, which extended upward between the muscles of the thigh and appeared to connect with an abscess near the pelvis. Blood count was 3,992,000 red cells; 9,500 leucocytes; 73 per cent. hemoglobin. Temperature varied from 99 to 100. After one month's treatment with potassium iodid and tonics internally, the patient left the hospital unimproved and died a few months later. No autopsy was held.

Blastomycetes were demonstrated in the pus from the abscess, and the organism was grown in pure culture.

CASE 17.—HYDE AND MONTGOMERY (previously unreported case): The patient was a machinist, 24 years old, a resident of Chicago. In 1899 the great toe of his left foot was amputated for what was supposed to be tuberculosis. Three weeks later severe pain appeared in the hip and persisted for three months. During this period a deep abscess formed in the middle of the thigh, opened, and discharged. The patient also had had pain in the right knee, followed by the formation of an abscess under the skin, which broke after two or three months, leaving an ulcer which has never entirely healed. During this period of activity of the disease he had some fever, lost a great deal in weight, became weak, thinks his left lung was affected, but does not remember having had cough or expectoration. After the first few months his general health gradually improved and the only lesion was the persistent ulcer on the outer surface of the right knee, which, after attaining the size of a dollar, remained stationary for years.

On examination, August, 1906, the outer surface of the knee showed a characteristic area of cutaneous blastomycosis. At this time the man was pallid and slightly anemic, but showed no other evidences of systemic disease. For eight months he was kept more or less constantly under the influence of potassium iodid, and the cutaneous ulcer was treated with *x*-ray, copper sulphate and other antiseptics. The patient's general health improved and the local lesion nearly disappeared. In July, 1907, his general health had again decidedly and rapidly deteriorated, and the knee had become very much swollen and presented a fistulous opening from which pus escaped. After a single visit to the dispensary he disappeared from observation, before a complete examination could be made.

Blastomycetes were demonstrated in smears and pure cultures obtained from the cutaneous lesions and from pus in the fistulous tract.

CASE 18.—OSWALD[23] (previously unreported case): The patient was a man with a cough and other evidences of a grave constitutional disorder; at the time

23. This case was seen by one of us (Ormsby) at the Alexian Brothers' Hospital, through the courtesy of Dr. Oswald and Dr. Louis Schmidt. The notes here given are necessarily incomplete and it is hoped that at a future date the case will be recorded in full.

of this visit he was very much emaciated, and very near death. There were cutaneous and large subcutaneous lesions on the face, chest, and other parts of the body, and several joints and a number of vertebræ were affected. On our visit that day the organism of blastomycosis was demonstrated in the sputum and in pus obtained from the knee joint, from a large subcutaneous abscess on the chest, and from a cutaneous lesion on the face.

Shortly after this the patient died, the autopsy being performed by Dr. W. A. Evans. We are informed that blastomycotic lesions occurred generally throughout the body, and that the bodies of several vertebræ were practically destroyed, together with some of the spinal cord.

Pure cultures were obtained by Dr. Jerger, who also demonstrated the pathogenicity of the organism for guinea-pigs, and the absence of tuberculosis in the case.

CASE 19.—KROST, MOES AND STOBER:[24] The patient, Polish laborer, and resident of United States four years, entered the Cook County Hospital April 8, 1907. The present disorder began four months before, as a severe cold with cough and expectoration, followed shortly by pain in the back. A month later a swelling appeared on the dorsal region at the left of the median line. Cough and expectoration increased; the appetite was poor; the patient lost in weight; and at the end of six weeks general weakness prevented his continuing at work. Two months after the beginning, a painful swelling developed on the dorsum of the left hand and foot, and over the left eleventh rib; a warty growth appeared at the right ala of the nose, followed by enlargement of both submaxillary glands.

Examination on admission revealed, in addition to the above findings, anemia; dulness over the left lower lobe; bronchophony with râles; a little enlargement of the heart; inguinal adenopathy; and slight temperature. There were small papillomatous growths on the forehead and right forearm. Blastomycetes were demonstrated in pus from the subcutaneous swellings, in the sputum, and in the urine, which chowed also a few casts and leucocytes. (The autopsy showed that the organisms in the urine came from the prostate gland.) Several blood counts showed leucocytes from 14,200 to 29,800, with hemoglobin about 70 per cent. The patient steadily lost strength; pain increased; sputum became more abundant, mucopurulent, and at times bloody; there was profuse sweating; and new abscesses appeared on different portions of the body. The patient died June 14, 1907.

Autopsy showed miliary and nodular blastomycosis of the lungs, kidneys, spleen, cerebrum, pleura and lymph glands; ulcerative blastomycosis of the cerebrum, cerebellum, prostate, pleura and skin; multiple abscesses of the osseous, muscular and subcutaneous tissues; parenchymatous nephritis; fatty changes, adenoma, and angioma of the liver; adenoma of the thyroid; general lymphatic hyperplasia; shaven-beard appearance of Peyer's patches; atrophy of the testicles; fibrous pleuritis. Some of the subcutaneous abscesses were six inches in diameter, and extended deep into the muscular tissue. There were abscesses limited to bony structures; others burrowed into surrounding soft structures. Erosions and more deeply seated destructive changes occurred in the bones of the hand and the feet, the sternum, ribs and vertebræ. The presence of large numbers of myelocytes in the blood led Drs. Krost, Moes and Stober to the belief that the medulla of other bones was probably invaded. The deep cervical and inguinal glands were much enlarged; the superficial cervical, submaxillary, and axillary glands were slightly larger than normal.

A histologic examination of the affected areas in the bones, joints, and internal organs, including the cerebrum, cerebellum and prostate gland, demonstrated the

24. Krost, R. A., Moes, M. J., and Stober, A. M.: Systemic Blastomycosis, Jour. Am. Med. Assn., 1908, l, 184.

presence of blastomycetes, together with the granulomatous structure usually seen in blastomycosis.

Pure cultures of the organism were obtained during the patient's life from the blood, various abscesses, and cutaneous lesions, and postmortem from the knee joint, spleen, and pleura, and a mixed culture from the prostate. No tubercle bacilli could be found in the sputum, pus, or tissue.

CASE 20.—CHURCHILL AND STOBER:[25] The patient, a Polish laborer, 39 years old, employed for the past four years in scrubbing and dusting Pullman cars, entered the Cook County Hospital, May 14, 1907. For three months he had suffered pain in the right side of the head and face, most marked over the malar prominence. Later, pain aggravated by movement appeared in the right hip and knee, above the shoulders, and in the left wrist. The knee and wrist became very much swollen and exceedingly tender. From the begining he had a moderate cough with occasional blood-stained sputum. There was marked loss of vision in the right eye.

Examination showed the patient to be markedly emaciated; twenty pounds under his average weight; his temperature 101, with physicial signs of beginning consolidation of the right upper lobe. The right hip, knee, and sternoclavicular joints were swollen, red, and painful. Over the knee there was fluctuation. The right great toe contained an abscess, which discharged thick, blood-stained pus. Scattered over the body were numerous pustular lesions and fourteen subcutaneous abscesses (one under the scalp) varying in size from one to five centimeters in diameter. The conjunctiva of the right eye was red and edematous. The patient was given potassium iodid, but apparently without effect. He had an irregular temperature with profuse sweats; pulse and respiration were rapid. The abscesses slowly enlarged, and the patient died of gradual exhaustion, June 20, 1907.

Autopsy showed serofibrinous pleuritis; pericarditis; purulent bronchitis; parenchymatous degeneration of the kidneys and liver; fibroid induration of the lungs; fibroid pleuritis; miliary blastomycotic nodules of the lungs, pleura, kidneys, spleen, peribronchial lymph glands; multiple blastomycotic abscesses of the lung, prostate, and the osseous, muscular, and subcutaneous tissues; multiple blastomycotic ulcers of the skin; blastomycosis of the right eye.

Pure cultures of blastomycetes were recovered from the vitreous humor of the eye by aspiration. Blastomycetes were also recovered from the pericardial fluid, pleural fluid, and various abscesses, including the prostatic abscess; streptococci were recovered from the heart blood. Blood cultures, as well as examination of the sputum and urine, showed neither blastomycetes nor tubercle bacilli.

CASE 21.—LEWISON AND JACKSON:[25] The patient, an Italian boy, aged 17, an organ-grinder and machine-shop helper, entered the Cook County Hospital May 20, 1907. Five months before this an abscess appeared in the middle of the right thigh, ruptured in two weeks, and discharged a thick, dark-brown pus. The resulting ulcer soon became covered with a heavy crust. Two months later the right knee joint became the seat of pain, limitation of motion, and later, of swelling. The following month the left knee became similarly involved, and subsequently the left ankle, both elbows, left wrist, and the first metacarpophalangeal joint of the left hand. One month after the first joint symptoms, subcutaneous abscesses and crust-covered ulcers began to appear on the face and scalp.

25. To be reported in the Cook County Hospital Reports. We are indebted to Dr. Stober for notes of Cases 20, 21 and 22.

On examination, the patient was found to be anemic, poorly developed, and suffering with great pain and stiffness in the joints. Slight changes from normal were detected in the physical examination of the lungs. The urine was practically negative. The blood examination showed leucocytes 9,600, cultures negative. The temperature varied from 101 to 103.6; respirations and pulse were both rapid. With tonic treatment and potassium iodid great improvement occurred, and the patient was discharged July 8, but was readmitted in ten days, with a sharp recurrence of all symptoms. This time better results were obtained with cupric sulphate used both locally and internally and on August 17 he was discharged a second time in fairly good condition, though he was not well and not free from cutaneous, subcutaneous, and joint lesions.

Blastomycetes were demonstrated in the abscesses, also later in the sputum. Tubercle bacilli were not found.

CASE 22.—MEYERS AND STOBER:[25] The patient, 20 years old, was a clerk in Chicago, but had been employed some months before as a laborer on a dredge in Arkansas and Iowa. He was admitted to Cook County Hospital May 8, 1907, in the service of Dr. Ryerson. For four months he had been ill, suffering with pain, shortness of breath, chills and fever, and occasional night sweats. For a month he had pain in the right external malleolus, which was worse at night. The leg had become swollen and tender. He had some patches on the face which he had been told were lupus spots.

On examination the patient was seen to be poorly developed, anemic, and emaciated. There were some evidences of consolidation of the lower lobe of the lung. The temperature was normal; the urine examination negative. On the neck was a large, soft, fluctuating mass. A large number of reddish areas, looking as though they contained pus, and abscesses of varying sizes, were present on different parts of the body. The right external malleolus was swollen, red, tender and painful. Several joints were similarly involved but to less extent. On opening and draining the swelling over the malleolus, necrotic bone was exposed. The patient slept but little, complaining of pain, especially at night. His temperature varied, ranging as high as 102.6.

Blastomycetes were demonstrated in pus from a number of unbroken abscesses and were obtained in pure culture.

SUMMARY—PROBABLE CASES.

CASE 23.—HYDE AND MONTGOMERY:[26] The patient was a male, aged 47, a resident of Chicago and a sewer-builder. At the time this case was reported, large areas of cutaneous blastomycosis existed upon the arms and forearms. Under treatment the areas nearly disappeared, but returned on his neglecting treatment, as he did for many months at a time. About four years after the beginning of his trouble he reappeared, after a long absence, with much more extensive and severe cutaneous lesions than ever before, and with fever, cough, anorexia, and marked general weakness, the symptoms pointing strongly to systemic infection with blastomycosis. He disappeared from view and died soon after in the poorhouse, where the nature of his disease was not recognized, and no autopsy was obtained.

CASE 24.—HYDE AND MONTGOMERY:[27] The patient was a well-to-do woman, 56 years of age, and a resident of Chicago. In November, 1901, she experienced a severe mental shock. Three weeks later a lesion appeared on the dorsal surface

26. Hyde and Montgomery: (reported as a case of cutaneous blastomycosis), Jour. Cutan. Dis., 1901, xix, 49.

27. Hyde and Montgomery: Cutaneous Blastomycosis, Jour. Am. Med. Assn., 1902, xxxviiii, 1486.

of the left hand, and within two weeks other lesions appeared on the left cheek, left heel, right leg, right big toe, right foot and left arm. Some of these began as "pimples," others as small nodules deep in the skin. At the same time subcutaneous nodes varying from the size of a bean to that of a walnut appeared over different portions of the breast, thorax and left thigh. These subcutaneous swellings became slightly red on the surface and very sensitive to the touch, but gradually underwent resolution without abscess formation. In January, lesions appeared on the upper lip and on the right index finger.

The cutaneous lesions were characteristic clinically and histologically of cutaneous blastomycosis. The organisms were demonstrated and recovered in cultures from the lesions. Large doses of potassium iodid and the *x*-ray were employed, and the patient made a complete recovery. Looking at this case in the light of recent experience it is highly probable that the multiple, somewhat widely disseminated, subcutaneous nodes were blastomycotic in origin.

CASE 25.—HYDE AND MONTGOMERY (previously unreported case): The patient was a successful business man of unusually robust appearance, 58 years old, and a resident of Illinois. In October, 1904, he caught a cold accompanied by headache, cough, some expectoration, soreness in the chest, and general weakness. On November 17 he went to bed and called a physician for the first time. The symptoms suggested a possible pneumonia. Ten days after going to bed, the pain in his chest became more marked and an abscess formed, which, on December 4, opened just below the upper border of the sternum and discharged a large quantity of pus. The patient slowly recovered his health, being confined to the house two months. On examination, Jan. 30, 1905, there was found a small fistula one inch in length lying across the sternum, and characteristic lesions of cutaneous blastomycosis on the right cheek and on the dorsum of the right hand. These appeared at first as lumps beneath the skin a few weeks after he began to feel bad. The patient stated that he felt fairly well, but was twenty pounds under weight. Examination of the chest by Dr. Joseph Capps disclosed signs of moderate infiltration of the apex of the right lung.

His physician reported the patient's complete recovery after two and one-half months of treatment with potassium iodid and radiotherapy.

Blastomycetes were demonstrated in smears and obtained in pure cultures from the miliary abscesses in the borders of the cutaneous lesions.

The symptoms and course of the illness, the recovery under treatment with the iodid of potassium, and the subcutaneous origin of the cutaneous lesions, all indicate strongly a case of systemic blastomycosis from which the patient made a full recovery.

CASE 26.—ALBERS:[28] The patient was a Wisconsin farmer, 64 years of age, a Scandinavian by birth. In July, 1906, he began to suffer from pain in the chest and abdomen, sore throat, cough, dysuria, anorexia and loss of strength. He was emaciated; his pulse was weak and irregular; but his temperature was normal, and physical findings relative to the lungs were negative. The skin lesions are described as raised, hyperemic spots, or pimples, somewhat larger than an ordinary pimple, scattered over the body.

Specimen of bloody, tenacious sputum sent to the laboratory for examination contained no tubercle bacilli, but many blastomycetes. The organism was obtained from the sputum in almost pure culture.

The subsequent history of the patient was not obtainable.

CASE 27.—EASTMAN AND KEENE:[29] The patient was a woman who stated that she had suffered for six weeks with what she termed "boils." The first one

28. Albers: Tr. Chicago Path. Soc., March 1, 1907.

29. Eastman and Keene: Ann. Surg., November, 1904.

appeared as a small, hard lump about the size of a pea on the back of her left hand. It grew to the size of a small pigeon-egg and then gradually disappeared. It was accompanied by no sensations, nor was there any discoloration of the skin. A few days after this had disappeared the patient noticed beneath the skin near the elbow a hard, globular body, about one and one-half inches in diameter. This at first was similar to the growth on the back of the hand. It, however, gradually increased in size until she opened it with a needle, when a thin, grayish, watery substance escaped. Budding blastomycetes were found in the discharge, which had persisted up to the time of her examination. In the axilla was a similar lesion, the size of a hen's egg, which later broke down and discharged.

The patient was the mother of a girl whom Drs. Eastman and Keene had been treating for a wound that was the seat of a mixed infection with *Bacillus pyocyaneus* and blastomycetes.

The mother stated that her son, 19 years old, had at the same time a similar lesion on his hip. A small kernel appeared beneath the skin, grew to the size of a hen's-egg, broke, and was discharging. Eastman and Keene conclude that there were three members in one family infected with blastomycetes.

(Unfortunately, the nature of the lesions on the boy's hip was undetermined, and the possibility in the mother's case of secondary infection with a yeast fungus of an ordinary open and discharging ulcer can not be eliminated.)

100 State Street.

BLOOD PRESSURE IN ONE HUNDRED CASES OF TUBERCULOSIS AT HIGH ALTITUDE.

LEROY S. PETERS, M.D.
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In recent years much has been written concerning blood pressure and its relation to many pathologic conditions. Its relation to tuberculosis has been discussed by many writers, but in all the literature I have failed to see any reports from sanatoria situated at high altitudes.

From the observations made here in the New Mexico Cottage Sanatorium, at an altitude of 6,000 feet, we are led to believe that altitude has an important influence on blood pressure. As will be shown in the course of this article, our average pressure is far higher than that at lower elevations or at sea level; and this, too, as a rule, with cases in the far advanced stages of the disease. Here the majority of our cases fall into this class; for it is a fact that in the west, nowadays, we see mostly advanced cases or those in whom the disease has made such inroads that a cure, according to the eastern standard of prognosis in tuberculosis, is difficult, if not impossible, of attainment. Yet, contending with these disadvantages, we turn out, class for class, as many, if not more, cures than the eastern and northern sanatoria.

It is at least worthy of suggestion that our results may be partly due to the stimulating effect of the dry mountain air, which increases the blood pressure through the building up of the general circulation. The results of blood-pressure observations in our cases, far from being indicative of tuberculosis, would signify almost perfect health; in fact, as a diagnostic sign blood pressure plays a minor rôle. It is far more valuable as a prognostic indication.

The following observations were made on a series of 100 cases at the New Mexico Cottage Sanatorium at an elevation of 6,000 feet. The pressure was taken with a Janeway sphygmomanometer with the cuff applied to the left arm above the elbow, the patient in a sitting posture, the forearm flexed on a level with the heart. The systolic pressure alone was recorded, since for all practical purposes we feel that this is sufficient.

The observations were made between the hours of 9 and 10 in the morning. Pressures were taken at different hours throughout the day, but only a slight difference in the reading was to be noted.

GENERAL TABLE 1.

Number.	Blood Pressure.	Pulse.	Hemoglobin.	Previous Infections.					Alcohol.	Age.	Sex.	Temperature.	Kidney Diseases.	Heart Lesions.	Degree of Involvement.
				Gonorrhea.	Syphilis.	Typhoid.	Pneu.	Diph.							
1.	126	80	12.878	—	—	—	—	—	—	32	M.	98.6	No.	—	III
2.	109	90	12.878	..	..	—	—	—	—	18	F.	98.6	No.	—	III
3.	104	80	14.522	—	—	—	—	—	—	25	M.	98.6	No.	—	II
4.	124	76	13.7	+	—	—	—	—	—	27	M.	98.6	Albumin. Casts.	—	III
5.	110	80	13.7	—	—	—	+	—	+	27	M.	100.	No.	—	II
6.	104	140	9.864	—	—	—	—	—	—	27	M.	102.	Albumin. Casts.	—	III
7.	130	?	9.59	..	..	—	—	—	—	43	F.	99.	No.	—	III
8.	116	85	11.508	..	..	—	—	—	+	22	F.	98.6	No.	—	I
9.	142	80	14.659	—	—	—	+	—	+	28	M.	99.	Casts.	—	III
10.	116	84	13.7	—	—	—	—	—	+	31	M.	98.6	No.	—	II
11.	128	80	13.7	—	+	—	—	—	+	25	M.	98.6	No.	—	I
12.	121	80	13.7	—	—	—	—	+	—	18	M.	98.6	No.	—	I
13.	100	104	13.7	—	—	+	—	—	+	33	M.	99.6	Albumin. Casts.	—	III
14.	132	100	12.33	—	—	+	—	—	+	54	M.	98.6	No.	—	III
15.	112	100	13.7	—	—	—	—	—	—	29	M.	101.	No.	—	III
16.	148	84	13.7	—	—	—	—	—	+	47	M.	98.6	No.	—	I
17.	119	70	13.7	..	..	—	—	—	—	24	F.	98.6	No.	—	I
18.	130	90	13.7	—	—	—	—	—	—	29	M.	99.	No.	—	III
19.	94	84	13.7	—	—	—	—	—	+	32	M.	98.6	No.	—	III
20.	104	80	13.7	..	..	—	—	—	—	23	F.	98.6	No.	—	I
21.	130	75	14.385	+	—	—	+	—	—	23	M.	98.6	No.	—	II
22.	112	102	11.645	—	—	—	—	—	—	35	M.	98.6	Albumin.	—	III
23.	120	98	14.796	—	—	—	—	—	—	22	M.	98.6	No.	—	III
24.	124	80	13.7	—	—	+	—	—	+	37	M.	98.6	No.	—	III
25.	117	128	13.7	+	—	—	—	—	—	24	M.	98.6	No.	—	I
26.	130	74	13.7	—	—	—	—	—	—	25	M.	98.6	No.	—	I
27.	119	80	13.7	..	..	—	—	—	—	28	F.	98.6	No.	—	III
28.	140	104	13.7	..	..	—	—	—	—	44	M.	98.6	No.	—	III
29.	110	90	13.7	—	+	—	—	—	—	37	M.	98.6	No.	—	III
30.	118	100	13.7	—	—	+	—	—	—	42	M.	98.6	No.	—	II
31.	150	100	13.7	+	+	+	—	—	+	30	M.	98.6	No.	—	II
32.	176	80	13.7	—	—	—	—	—	—	28	M.	99.4	Albumin. Casts.	—	II
33.	110	120	13.7	—	—	—	—	—	—	28	M.	98.6	No.	—	III
34.	144	90	13.7	+	—	+	+	—	+	40	M.	99.	Albumin.	—	III

GENERAL TABLE 1.—Continued.

Number.	Blood Pressure.	Pulse.	Hemoglobin.	Previous Infections.					Alcohol.	Age.	Sex.	Temperature.	Kidney Diseases.	Heart Lesions.	Degree of Involvement.
				Gonorrhea.	Syphilis.	Typhoid.	Pneu.	Diph.							
35.	120	75	13.974	—	—	—	—	+	+	48	M.	98.6	Casts.	—	II
36.	100	76	13.7	+	—	—	+	—	+	29	M.	98.6	No.	—	I
37.	140	88	13.974	—	—	—	—	—	+	25	M.	98.6	No.	—	I
38.	122	90	11.371	..	..	+	—	—	—	19	F.	98.6	No.	—	II
39.	130	80	13.7	—	—	—	—	—	—	27	M.	99.	Casts.	—	III
40.	130	90	14.111	—	—	—	—	—	—	22	M.	98.6	Casts.	—	I
41.	150	90	12.878	+	—	—	—	—	—	29	M.	98.6	Casts.	—	I
42.	94	100	11.508	—	—	+	—	—	+	25	M.	99.8	No.	—	III
43.	100	90	13.015	+	—	—	—	—	+	23	M.	98.6	Casts.	—	III
44.	112	85	13.837	+	—	—	+	—	—	28	M.	98.6	No.	—	II
45.	118	122	12.31	+	—	—	—	—	—	21	M.	99.2	Albumin. Casts.	—	II
46.	172	95	13.837	+	+	—	—	—	+	40	M.	99.	Casts.	—	III
47.	136	90	13.563	+	—	—	—	—	+	25	M.	98.6	No.	—	I
48.	160	95	11.782	+	—	—	—	—	—	40	M.	100.	Casts.	—	II
49.	110	80	13.7	—	—	+	—	—	—	34	M.	98.6	Casts.	—	II
50.	100	90	13.152	—	—	—	—	—	—	23	M.	98.6	Casts.	—	I
51.	140	84	12.741	..	..	—	—	—	—	52	F.	98.6	No.	—	II
52.	142	90	13.7	—	—	—	+	—	—	24	M.	98.6	Casts.	—	I
53.	118	92	13.7	—	—	—	—	—	+	58	M.	98.6	No.	—	II
54.	130	84	11.645	..	..	—	—	—	—	20	F.	98.6	Casts.	—	III
55.	100	112	13.7	+	+	—	—	—	+	28	M.	99.4	Casts.	—	III
56.	130	70	12.33	+	—	—	—	—	+	23	M.	99.	Casts.	—	III
57.	164	138	13.7	—	—	—	—	—	+	52	M.	99.	Albumin. Casts.	—	III
58.	136	100	13.7	—	—	+	+	—	—	49	M.	98.6	Albumin. Casts.	—	III
59.	120	120	10.96	+	—	—	—	—	—	20	M.	100.	No.	—	III
60.	120	108	14.345	—	—	—	—	—	—	28	M.	98.6	Casts.	—	I
61.	120	108	13.974	..	..	+	+	—	+	35	F.	98.6	No.	—	II
62.	110	110	12.741	..	..	—	—	+	—	33	F.	98.6	No.	?	II
63.	110	92	12.467	..	..	—	—	—	—	22	F.	98.6	No.	—	III
64.	124	100	13.7	—	—	+	—	—	—	31	M.	98.6	No.	—	III
65.	150	84	12.33	+	—	—	—	—	—	48	M.	99.1	Albumin. Casts.	?	III
66.	120	85	13.563	—	—	+	—	—	—	24	M.	98.6	Casts.	—	III
67.	128	120	12.33	..	..	—	—	—	—	42	F.	99.	Albumin. Casts.	—	III
68.	130	80	14.248	+	—	—	+	—	+	40	M.	98.6	Casts.	—	III

GENERAL TABLE 1.—Continued.

Number.	Blood Pressure.	Pulse.	Hemoglobin.	Previous Infections.					Alcohol.	Age.	Sex.	Temperature.	Kidney Diseases.	Heart Lesions.	Degree of Involvement.
				Gonorrhea.	Syphilis.	Typhoid.	Pneu.	Diph.							
69.	158	100	12.878	..	..	—	+	+	—	36	F.	98.6.	No.	—	I
70.	130	88	13.015	..	..	—	—	+	—	27	F.	98.6	Casts.	—	III
71.	100	80	10.965	+	—	—	—	—	—	38	M.	99.4	Casts.	—	II
72.	128	75	14.111	+	—	+	—	—	—	27	M.	98.6	No.	—	III
73.	128	75	13.974	—	—	—	—	—	+	32	M.	98.6	No.	—	II
74.	136	80	13.7	—	—	—	+	—	—	24	M.	98.6	Casts.	—	III
75.	140	80	13.289	..	..	—	—	—	—	30	F.	98.6	No.	—	I
76.	120	100	12.33	+	+	—	—	—	+	40	M.	99.2	No.	—	III
77.	144	80	12.33	—	—	—	—	+	+	46	M.	98.6	No.	—	II
78.	158	85	12.604	+	—	—	+	—	+	35	M.	99.	Albumin. Casts.	—	II
79.	118	75	10.275	—	—	—	—	—	—	35	M.	99.5	No.	—	II
80.	122	110	9.59	—	—	—	—	—	+	35	M.	98.6	No.	—	III
81.	130	80	15.7	+	—	—	—	—	—	29	M.	98.6	No.	—	I
82.	142	120	10.125	+	—	—	—	—	—	45	M.	99.	No.	—	II
83.	146	80	13.562	—	—	+	—	—	—	42	M.	98.6	Casts.	—	III
84.	96	80	14.242	+	—	—	—	—	+	26	M.	98.6	No.	—	II
85.	120	80	13.7	—	—	—	—	—	—	25	M.	98.6	No.	—	III
86.	90	75	13.563	—	—	—	—	—	—	22	M.	98.6	No.	—	I
87.	118	100	13.7	—	—	—	—	—	—	28	F.	98.6	Casts.	—	III
88.	120	100	13.7	—	—	—	—	—	—	39	M.	98.6	No.	—	III
89.	126	85	14.657	—	—	—	—	—	—	28	M.	98.6	No.	—	III
90.	108	90	13.7	..	..	+	—	—	—	40	F.	100.	Albumin. Casts.	—	III
91.	134	85	14.248	+	—	—	—	—	+	37	M.	98.6	No.	—	III
92.	124	85	12.407	—	—	—	—	—	+	25	M.	98.6	No.	—	III
93.	128	75	14.237	—	—	+	—	—	—	23	M.	98.6	Casts.	—	I
94.	135	85	13.7	+	—	—	—	—	+	26	M.	98.6	No.	—	I
95.	122	90	14.522	..	..	—	—	—	—	36	F.	98.6	No.	—	II
96.	106	120	13.152	—	—	—	—	—	—	34	M.	99.4	No.	—	III
97.	108	100	12.741	—	—	—	+	—	+	47	M.	99.4	Albumin. Casts.	—	III
98.	130	100	12.33	..	..	—	—	+	—	18	F.	98.6	No.	—	II
99.	138	88	12.33	..	..	—	+	—	—	27	F.	98.6	No.	—	I
100.	146	80	10.412	+	—	—	—	—	+	28	M.	98.6	Albumin. Casts.	—	III

* Mitral regurgitation. † Aortic Stenosis.

We have taken into consideration pulse, hemoglobin, previous infections—such as gonorrhea, syphilis, typhoid fever, pneumonia and diphtheria—the use of alcohol, age, sex, temperature, heart lesions and kidney disease.

As will be noted in the table, we did not take into account venereal infections in women, for in an institution of this kind the women would either be innocent of such infection or would fail to give a correct report.

General Table 1 gives in outline the results of our investigations.

A detailed study of the facts noted in the general columns shows some interesting relations, which will now be grouped separately.

PULSE RATE AND BLOOD PRESSURE.

Pulse.	Pressure.
75	80- 90
91	90-100
98	100-110
95	110-120
88	120-130
90	130-140
89	140-150
91	150 and over.

In the series from 80-90 pressure we had only one case, which does not admit of any conclusion. However, the remainder of the results show that there is no relation between the pulse rate and blood pressure.

HEMOGLOBIN AND BLOOD PRESSURE.

The estimation of hemoglobin was made with a von Fleischl instrument, the results recorded in the percentage of hemoglobin in 100 grams of blood.

Hemoglobin.	Pressure.
13.563	80- 90
13.124	90-100
13.12	100-110
13.195	110-120
13.234	120-130
13.3	130-140
12.934	140-150
13.083	150 and over.

That the hemoglobin averages practically normal for all pressures may be seen at a glance. At this altitude and in this climatic environment anemia is relatively an insignificant factor in tuberculosis.

PREVIOUS INFECTIONS AND BLOOD PRESSURE.

Gonorrhea.

No. cases	28
Av. pressure	130
No. cases below 110	5
No. cases 110-145	16
No. cases over 145	7
Highest pressure	172
Lowest pressure	96

SYPHILIS.

No. cases	6
Av. pressure	130
No. cases below 110	1
No. cases 110-145	3
No. cases over 145	2
Highest pressure	172
Lowest pressure	100

TYPHOID FEVER.

No. cases	18
Av. pressure	123
No. cases below 110	3
No. cases 110-145	13
No. cases over 145	2
Highest pressure	150
Lowest pressure	94

PNEUMONIA.

No. cases	15
Av. pressure	131
No. cases below 110	2
No. cases 110-145	11
No. cases over 145	2
Highest pressure	158
Lowest pressure	100

DIPHTHERIA.

No. cases	7
Av. pressure	130
No. cases below 110	0
No. cases 110-145	6
No. cases over 145	1
Highest pressure	158
Lowest pressure	110

Here it is hard to draw definite conclusions in the venereal cases, for we usually find other factors entering to influence the pressure. Judging from the results as shown in the table, we are inclined to believe that preceding gonorrhea, syphilis, pneumonia, diphtheria and typhoid fever do not tend to raise the blood pressure.

ALCOHOL AND BLOOD PRESSURE.

No. cases	36
Av. pressure	127
No. cases below 110	8
No. cases 110-145	22
No. cases over 145	6
Highest pressure	172
Lowest pressure	94

This includes both moderate drinkers and those who have drunk to excess. The average would hardly justify one in saying that drinking increased the pressure.

AGE AND BLOOD PRESSURE.

AGE 15-25.

No. cases	21
Av. pressure	120
No. cases below 110	5
No. cases 110-145	15
No. cases over 145	1
Highest pressure	150
Lowest pressure	90

AGE 25-40.

No. cases	57
Av. pressure	121
No. cases below 110	10
No. cases 110-145	41
No. cases over 145	6
Highest pressure	176
Lowest pressure	94

AGE 40-60.

No. cases	22
Av. pressure	136
No. cases below 110	2
No. cases 110-145	14
No. cases over 145	6
Highest pressure	172
Lowest pressure	108

AGE 60 AND OVER.

No. cases	0

This shows conclusively that, in our patients, blood pressure tends to increase with advancing age. It is of interest to compare our records with those of Thayer for normal and tuberculous cases. Our records in far advanced cases compare very favorably with his for normal cases.

THAYER'S CASES.			OUR CASES.
AGE.	NORMAL.	T. B. CASES.	T. B. CASES.
10-20	128.7	100.33	122
20-30	136.9	101	123
30-40	140.8	94	124
40-50	142.2	105.5	134
50-60	154.8	105	138
60 and over	180	114	No cases

SEX AND BLOOD PRESSURE.

MALE.

No. cases	79
Av. pressure	126
No. cases below 110	14
No. cases 110-145	53
No. cases over 145	12
Highest pressure	176
Lowest pressure	90

FEMALE.

No. cases	21
Av. pressure	124
No. cases below 110	3
No. cases 110-145	17
No. cases over 145	1
Highest pressure	158
Lowest pressure	104

Although there is but slight difference in the two pressures, yet the results correspond to those obtained by other observers, that the pressure in the female is a little lower than that in the male.

TEMPERATURE AND BLOOD PRESSURE.

TEMPERATURE NORMAL.

No. cases	72
Av. pressure	124
No. cases below 110	9
No. cases 110-145	56
No. cases over 145	7
Highest pressure	158
Lowest pressure	90

TEMPERATURE 99-100.

No. cases	22
Av. pressure	131
No. cases below 110	6
No. cases 110-145	11
No. cases over 145	5
Highest pressure	176
Lowest pressure	94

TEMPERATURE 100-101.

No. cases	4
Av. pressure	124
No. cases below 110	1
No. cases 110-145	2
No. cases over 145	1
Highest pressure	160
Lowest pressure	108

TEMPERATURE 101 AND OVER.

No. cases	2
Av. pressure	108
No. cases below 110	1
No. cases 110-145	1
No. cases over 145	0
Highest pressure	112
Lowest pressure	104

Our cases run for the most part a normal temperature, the pressure also being about normal. The cases with high temperature are too few to justify an opinion. However, one is led to believe that the higher the temperature the lower the blood pressure is apt to be.

HEART DISEASE AND BLOOD PRESSURE.

No. cases	2
Av. pressure	130

The number of cases would not justify an opinion.

KIDNEY DISEASE AND BLOOD PRESSURE.

No. cases	37
Av. pressure	131
No. cases below 110	8
No. cases 110-145	20
No. cases over 145	9
Highest pressure	176
Lowest pressure	100

Although other observers seem to believe that the type of nephritis which usually complicates tuberculosis, plays no part in increasing pressure, our results point to the fact that it does. In our cases in fairly good physical condition the pressure was very high, the lowered average being due to a few cases in which the toxemia was very marked, and in which the pressure was naturally low.

DEGREE OF INVOLVEMENT AND BLOOD PRESSURE.

In determining the degree of involvement we have followed Turban's classification and indicated the extent of the lesion by the Roman numerals I, II, III, corresponding roughly to incipient, moderately advanced and far advanced cases.

INVOLVEMENT.—I.

No. cases	23
Av. pressure	128
No. cases below 110	4
No. cases 110-145	15
No. cases over 145	4
Highest pressure	158
Lowest pressure	90

INVOLVEMENT.—II.

No. cases	26
Av. pressure	126
No. cases below 110	3
No. cases 110-145	19
No. cases over 145	4
Highest pressure	176
Lowest pressure	96

INVOLVEMENT.—III.

No. cases	51
Av. pressure	124
No. cases below 110	10
No. cases 110-145	36
No. cases over 145	5
Highest pressure	172
Lowest pressure	94

GENERAL TABLE 2.

Case.	B. P. on Admission.	B. P. on Discharge.	Status on Admission.	Status on Discharge.	Case.	B. P. on Admission.	B. P. on Discharge.	Status on Admission.	Status on Discharge.
1.	106	126	III	Arrested.	51.	122	140	II	Apparently cured.
2.	101	109	III	Improved.	52.	130	142	I	Improved.
3.	102	118	II	Improved.	53.	110	126	II	Apparently cured.
4.	112	124	III	Improved.	54.	130	130	III	Improved.
5.	100	91	II	Progressive.	55.	110	100	III	Progressive.
6.	104	98	III	Progressive.	56.	130	128	III	Improved.
7.	130	...	III	.....	57.	164	150	III	Unimproved.
8.	108	116	I	Apparently cured.	58.	136	144	III	Arrested.
9.	125	142	III	Arrested.	59.	120	120	III	Improved.
10.	113	116	II	Arrested.	60.	110	130	I	Apparently cured.
11.	128	102	I	Unimproved.	61.	128	130	II	Improved.
12.	121	...	I	.....	62.	110	102	II	Progressive.
13.	100	106	III	Progressive.	63.	110	124	III	Improved.
14.	132	126	III	Unimproved.	64.	98	140	III	Improved.
15.	112	100	III	Progressive.	65.	134	140	III	Arrested.
16.	126	134	I	Arrested.	66.	128	134	III	Improved.
17.	103	104	I	Apparently cured.	67.	110	126	III	Improved.
18.	120	130	III	Improved.	68.	130	148	III	Arrested.
19.	94	90	III	Arrested.	69.	150	150	I	Apparently cured.
20.	104	...	I	.....	70.	106	120	III	Apparently cured.
21.	104	134	II	Arrested.	71.	88	110	II	Improved.
22.	112	...	III	.....	72.	119	128	III	Arrested.
23.	110	120	III	Arrested.	73.	110	128	II	Arrested.
24.	112	124	III	Arrested.	74.	100	126	III	Arrested.
25.	117	...	I	.....	75.	110	140	I	Apparently cured.
26.	130	132	I	Apparently cured.	76.	106	118	III	Improved.
27.	119	...	III	.....	77.	134	150	II	Improved.
28.	135	144	III	Arrested.	78.	148	160	II	Unimproved.
29.	102	110	III	Improved.	79.	118	140	II	Improved.
30.	118	110	II	Improved.	80.	122	...	III	.....
31.	120	150	II	Improved.	81.	130	134	I	Improved.
32.	134	176	II	Unimproved.	82.	144	148	II	Arrested.
33.	110	126	III	Arrested.	83.	146	154	III	Improved.
34.	134	144	III	Arrested.	84.	96	130	II	Improved.

GENERAL TABLE 2.—Continued

Case.	B. P. on Admission.	B. P. on Discharge.	Status on Admission.	Status on Discharge.	Case.	B. P. on Admission.	B. P. on Discharge.	Status on Admission.	Status on Discharge.
35.	114	120	II	Arrested.	85.	110	120	III	Apparently cured.
36.	86	120	I	Apparently cured.	86.	88	112	I	Arrested.
37.	122	128	I	Apparently cured.	87.	112	112	III	Progressive.
38.	122	126	II	Improved.	88.	113	120	III	Arrested.
39.	122	130	III	Improved.	89.	102	126	III	Arrested.
40.	134	144	I	Arrested.	90.	108	108	III	Progressive.
41.	138	140	I	Arrested.	91.	114	134	III	Arrested.
42.	90	124	III	Improved.	92.	108	124	III	Arrested.
43.	120	110	III	Progressive.	93.	128	128	I	Apparently cured.
44.	110	110	II	Unimproved.	94.	130	135	I	Arrested.
45.	106	118	II	Improved.	95	102	122	II	Arrested.
46.	130	172	III	Arrested.	93.	106	116	III	Improved.
47.	134	130	I	Arrested.	97.	108	120	III	Improved.
48.	100	156	II	Unimproved.	98.	128	136	II	Improved.
49.	96	110	II	Apparently cured.	99.	130	138	I	Arrested.
50.	112	118	I	Improved.	100.	114	146	III	Improved.

Although 50 per cent. of our cases are in the far advanced stage of the disease, yet we believe that we have enough cases in the other stages to warrant an opinion. The difference in pressure in the three stages is so slight that we believe the degree of involvement and the blood pressure bear no relation to each other. However, that the blood pressure tends to increase with improvement in the pulmonary condition is shown by General Table 2. In this table we have reported the pressure both on admission and on discharge, and also have given the pulmonary status of the patient. In cases where the stay was of too short duration to get a fair estimate of the pressure we have omitted it altogether.

From General Table 2 the following relations may be noted:

APPARENT CURES.

No. cases 14
Av. pressure on admission 114
Av. pressure on discharge 127
Av. increase 13

ARRESTED.

No. cases	31
Av. pressure on admission	119
Av. pressure on discharge	132
Av. increase	13

IMPROVED.

No. cases	32
Av. pressure on admission	115
Av. pressure on discharge	128
Av. increase	13

UNIMPROVED.

No. cases	7
Av. pressure on admission	139
Av. pressure on discharge	140
Average increase	1

PROGRESSIVE.

No. cases	9
Av. pressure on admission	108
Av. pressure on discharge	103
Av. decrease	5

It is of interest to note that in all the cases showing improvement the average increase in pressure is 13 mm., while in the unimproved the pressure remains practically the same, and in the progressive shows a slight decrease.

HEMORRHAGE AND BLOOD PRESSURE.

A few cases of pulmonary hemorrhage have lately been reported in which the blood pressure was low; in fact, some observers go so far as to state that it is uniformly low.

We have had two cases under our care, and in both the blood pressure was low on admission—in one 90 and in the other 110. These cases were in the incipient and far advanced stages, respectively. The man with the 90 pressure started with a series of hemorrhages and continued to bleed at intervals for a period of six weeks. His pressure reached the 150 mark on the day the bleeding began and never came down lower than 130, except on the administration of amyl nitrite, and then only temporarily. The other went to 140 and stayed there until a short time before death. It might be well to say that the death was caused by great toxemia rather than by the loss of blood, for at no time did the bleeding exceed two ounces of pure blood. Of course, where there is great loss of blood the pressure would be necessarily low.

However, we can not draw conclusions from these two cases; the number is too small.

If it were true that during hemorrhage the blood pressure is higher, it would be interesting to determine why it is that, in a high altitude

with attending high blood pressure, hemorrhage should be a very infrequent manifestation of tuberculosis, as it certainly is with us. One or two hemorrhages a year, in an institution with from fifty to sixty patients, is about all we observe; and this one could not call a high percentage of hemorrhagic cases.

CONCLUSIONS.

Of course 100 cases is too small a number on which to base radical conclusions, but it certainly seems to us that this increase in blood pressure on coming into a high altitude may bear a direct relation to the possibility of the alleviation or cure of pulmonary tuberculosis when treated at high elevations.

It is generally recognized that heretofore an analysis of climatic factors, in an effort to explain their uses in the treatment of pulmonary tuberculosis, has been quite unsatisfactory. Our observation that blood pressure is raised by a residence in high altitudes may serve to explain a portion of the uses of climate in the treatment of tuberculosis.

It is usually conceded that *a posteriori* knowledge of the value of climate, especially high climate, in tuberculosis is already available; and it seems to us that, if a further investigation confirms our findings, we are now in possession of some of the *a priori* knowledge as well.

From our observations we draw the following conclusions:

1. Altitude has an important influence on blood pressure. The average pressure is higher here than at lower altitudes or at sea level.

2. There is little if any relation between blood pressure and pulse rate. The same holds true for hemoglobin.

3. Gonorrhea, syphilis, pneumonia, diphtheria and typhoid fever have no influence on blood pressure.

4. Alcohol has no effect on blood pressure.

5. Blood pressure increases with advancing age.

6. The pressure in the female is a little lower than that in the male.

7. Apparently the higher the temperature the lower the blood pressure.

8. A complicating nephritis tends to increase blood pressure.

9. The degree of involvement and the blood pressure bear no necessary relation to each other. The pressure tends to increase as the pulmonary condition improves.

10. The blood pressure is increased in pulmonary hemorrhage.

11. The blood pressure in tuberculosis is far more reliable as a prognostic than as a diagnostic sign.

THE SERUM DIAGNOSIS OF SYPHILITIC DISEASES.*

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Every new laboratory method requires confirmation from many workers before being accepted as an established aid to investigation. The Wassermann syphilis reaction seems now to have reached a stage where it can be used as an actual laboratory aid in diagnosis; and, therefore, as it has been but sparingly commented on in American journals, a brief account of its significance will not come amiss.

To make this reaction plain to every physician we begin with the main fact to be remembered, namely that all such biologic experiments are physicochemical in their essential nature. This does not imply, however, that the technic is as easy as an ordinary chemical experiment. In order that the reaction may be understood, moreover, certain terms must be made clear.

An antibody is the reaction product formed in the blood of an animal when a solution of some substance, toxic or otherwise, is injected into it. This antibody generally combines with the injected substance, called the antigen, to form a compound. If these compounds are insoluble it is called a precipitin. If the injected substance is a suspension of bacteria, and these bacteria are dissolved by the antibody, bacteriolysins are formed; if they are erythrocytes, hemolysins are formed, causing hemolysis or a "laking" of the blood. When we speak of an agglutinin we imply that the injected cells have been agglutinated and not dissolved.

In the complement tests we use as antigen or receptor a known substance, add to it the fluid we are testing and some guinea-pig serum. If the fluid to be tested is of like nature to the receptor we do not obtain hemolysis when this solution, properly prepared, is added to heated hemolytic rabbit serum and washed sheep's corpuscles. This is due to the fact that there has already been a binding of the complement, the antigen and the serum tested being homologous.

In 1901 Bordet and Gengou discovered that if emulsions of bacteria were mixed with inactivated immune serum and a complement added, this complement bound itself with the bacteria, with the result that any red blood corpuscle filled with its hemolytic amboceptor would not dissolve. This result was due to the fact that on account of the previous

*Read at the meeting of the Allegheny County Medical Society, June 16, 1908.

binding of complements the emulsions of bacteria were no longer available for the hemolytic amboceptor. Three years later, in 1905, Neisser and Sachs used this method for the detection of minute quantities of albumin.

Wassermann and Bruck, by successive steps, not only gave a clinical trend to these observations but succeeded in determining that extracts from infected organs could be used as well as solutions of bacterial extracts, a method which they first employed as an advance on Bordet and Gengou's original bacterial suspensions. These results led them, in conjunction with A. Neisser, to discover a serum diagnosis of syphilis —the Wassermann syphilis reaction.

They showed that in the serum of syphilitic apes there occurred a substance which was not present in normal serum, and later that when the blood serum of syphilitic individuals was added to extracts from the liver of a syphilitic new-born the complement was bound.

This reaction was confirmed by others, it being shown to be specific and almost invariably negative with sera from normal persons so that it could be looked on as being a reaction of amboceptor-like reaction products on substances which were directly connected with the original luetic infection and which must be present in extracts of syphilitic organs used for the complement fixation.

A number of later observations tended to show that it was not specific for the antigens of the syphilitic reaction, and, therefore, for the amboceptor nature of the serum contents specific for lues. Marie and Levaditi found that a similar reaction, though a weaker one, could be produced with extracts from normal liver. Weil, Plaut, Braun, Volk, Pötzl, Michaelis and others showed that antigens for luetic sera were found in non-luetic organs. Landsteiner and Müller discovered independently that lipoid substances, especially lecithin, as well as liver extracts, produced this reaction. Pötzl, Sachs and Altmann found that a sodium oleate solution also produced this reaction. Benecke utilized this discovery to explain the increased efficiency of fetal livers in the production of the reaction, as they contain many fat drops surrounded by an invisible soap membrane. He believes this fact to be confirmatory of Michaelis' opinion that Wassermann's reaction "does not reveal the presence of an antibody against the cause of syphilis or its poisons, but some other substance which has no direct connection with the cause of the syphilis, but which is found more abundantly in, or more easily extracted from, syphilitic organs than from normal ones."

Though Wassermann regarded this reaction at first as denoting the presence of an antibody, neither he nor his pupils, in their later conclu-

sions, regarded it as being indicative of the action of an antibody in the sense of a recuperative action (as in diphtheria). That the lipoid element in this reaction does not negative its value is readily apparent; on the contrary, it perhaps explains the lipoid degeneration in parasyphilitic diseases. The results in over 1,000 cases examined, in which the diagnostic value of the reaction was shown, surely inclines us to accept it as of value despite laboratory criticisms concerning its actual scientific foundation, for these results show that normal individuals never give the reaction, and about 80 per cent. of syphilitic cases do. Wassermann emphasizes especially the fact that it is a reaction only occurring with syphilitic serum, no matter of what nature the extracts which are used in conjunction with it, and that it is as important as the Widal reaction in typhoid fever.

It is probable that this reaction is that of a body formed in slight amounts in a healthy individual, which, however, defies detection until increased by syphilitic infection.

The alkalinity of the serum seems to have an influence in the reaction, it being prevented by 1/800 to 1/3200 sodium hydrate solution and increased by 1/1000 to 1/2000 hydrochloric acid solution (Sachs and Altmann). In this strength these reagents have no action on hemolysis. Never, however, did non-syphilitic serum become positive by the addition of hydrochloric acid solutions (lipoid action under lessened alkalinity).

Our technic, which was according to Wassermann and Sachs and Altmann, was briefly as follows: 4 to 5 c.c. of blood was obtained by venesection, 0.5 to 1 c.c. of serum being enough for four to five tubes with decreasing quantities of antigen. As antigen, we employed a freshly prepared 1 per cent. solution of sodium oleate in 0.85 per cent. sodium chlorid solution. This substance, in itself hemolytic, is inhibited by blood serum in proper proportions (Noguchi and Liebermann); and as Sachs and Altmann have showed, it prevents the hemolytic action of the complement. The anticomplement action of the blood serum plays no part in these experiments, as the complement fixation occurs below the inhibition zone in question. The difference between the inhibition of soap hemolysis by syphilitic and normal serum is slight; Sachs and Altmann found it so, and we can confirm their findings. The best amboceptor is the serum of a rabbit injected with calf's blood and rendered inactive by heating to 56 C.; this is known to hemolyze sheep's blood. Three injections of 50 to 80 c.c. of calf's blood intraperitoneally suffice in from two to three weeks to furnish a sufficiently strong hemolytic serum. Two to two and one-half amboceptor units are sufficient. It

is necessary to value accurately the hemolytic amboceptors used. The sheep's blood is washed several times with normal salt solution. To activate the amboceptor, fresh guinea-pig serum is used. The complement can be kept for about a week, if 1 per cent. sodium chlorid is added and then frozen. To carry out the reaction 0.6, 0.5, 0.4, 0.3, 0.25, 0.2, 0.1 c.c. of sodium oleate solution is employed (using tubes containing about 10 c.c.) and 1 c.c. of a 1 to 10 solution of guinea-pig serum and 1 c.c. of serum to be examined heated to 56 C. This is allowed to stand for one hour at 37 C. to bind the complement, then 0.5 of amboceptor thinned out to a 1:200 solution is added (2 to 3 amboceptor units) and 1 c.c. of 5 per cent. sheep's blood (normal salt solution). Each tube is filled to 5 c.c. with normal salt solution. The tubes are then kept at 37 C. in the thermostat and hemolysis observed for about two hours.

The inhibitory zone in our tests lay between 0.4 and 0.3 c.c. somewhat above the limits of Altmann and Sachs (0.25 c.c.). It is necessary to use a control test each time to determine this zone, as the sodium oleate varies somewhat in its dissolving power.

We give the results in a few of our cases to show how reactions are tabulated.

1% Sodium oleate Solution	Human Serum 1 : 10 Inactivated at 56 C for ½ hr.	+	Guinea-pig Serum 1 : 10	+	Rabbit amboceptor 0.5

HEMOLYSIS.

Solution.	Case. 1.	Case 2.	Case 3.	Case 24.	Case 31.
0.6	Complete.	Complete.	Complete.	Complete.	Complete.
0.5	Complete.	Complete.	Complete.	Complete.	Complete.
0.4	0	0	Complete.	0	Complete.
0.3	0	Trace.	Complete.	0	Complete.
0.25	0	Complete.	Complete.	0	Almost.
0.2	0	Complete.	Complete.	0	0
0.1	Trace.	Complete.	Complete.	0	Complete.
0.0	Complete.	Complete.	Complete.	Complete.	Complete.

CASE 1.—F. Paresis. History of syphilis. Reaction positive at 0.4.

CASE 2.—B. Paresis. History obscure. Reaction positive at 0.4.

CASE 3.—T. G. Tertiary syphilis. History negative. Reaction negative.

CASE 4.—G. H. Suspected syphilis. No symptoms. Reaction positive.

CASE 5.—T. S. Nocturnal epilepsy. Arteriosclerosis. Reaction negative.

CASE 6.—Mrs. G. R. Suspected syphilis. No symptoms. Husband syphilitic. Reaction positive.

CASE 7.—Secondary syphilis. Under mercurial treatment. Reaction negative.

CASE 8.—J. B. Paresis. Suspected syphilis. Reaction positive.

CASE 9.—J. F. Tabes dorsalis. No history of syphilis. Reaction positive.

CASE 10.—D. O. Tuberculosis. No history of syphilis. Reaction negative.

CASE 11.—J. R. R. Paresis. No history of syphilis. Reaction positive.

CASE 12.—J. P. Mc. Paresis. History of syphilis. Reaction positive.

CASE 13.—E. G. S. Paresis. No history of syphilis. Reaction negative.

CASE 14.—R. M. C. Tabes dorsalis. History not known. Reaction positive.
CASE 15.—G. H. E. Paresis. No previous history. Reaction negative.
CASE 16.—G. McC. Paresis. History of syphilis. Reaction positive.
CASE 17.—G. J. B. Paresis. No previous history. Reaction positive.
CASE 18.—T. L. Tertiary syphilis. No treatment. Reaction positive.
CASE 19.—G. H. Doubtful syphilis. No symptoms. Reaction negative.
CASE 20.—W. M. Tuberculosis. Reaction negative.
CASE 21.—Tertiary syphilis nineteen years ago. Chancre two months ago. Reaction positive.
CASE 22.—Secondary syphilis. Not treated. Reaction positive.
CASE 23.—Tertiary syphilis. Ulcers of nose and arm. Reaction positive.
CASE 24.—G. V. Incipient paresis. Reaction positive at 0.4.
CASE 25.—T. B. Tertiary lues. No symptoms. Reaction positive.
CASE 26.—G. W. Paresis. History of syphilis. Reaction positive.
CASE 27.—R. B. Paresis. History of syphilis. Reaction positive.
CASE 28.—R. K. Cerebral syphilis. Reaction positive.
CASE 29.—S. T. Chancre of penis. Spirochetes found. Reaction positive.
CASE 30.—D. M. Syphilitic orchitis. Syphilis in 1887. Reaction positive.
CASE 31.—N. M. Pseudoleukemia. Spirochætæ lymphaticæ. Reaction positive.

Our work, did we not look on it as being merely confirmatory of that of others, would not be conclusive, on account of our having used it with only thirty-one suspected syphilitic patients. In addition to these thirty-one, many others were selected from the surgical wards of the Allegheny General Hospital as absolutely non-syphilitic patients, and all of these were negative. Of the thirty-one cases, twelve were clinically diagnosed as paresis, and ten of these gave a positive reaction, two a negative. Two cases of tabes gave a positive reaction. Thirteen cases were either positive or suspicious cases of lues and three of these were negative. Three others were cases in which lues might have been in question, but all were negative. The last case was one of pseudoleukemia. Thus 75 per cent. of our cases gave a positive reaction. An idea of the significance of the reaction is shown by the outlines of some of our cases:

CASE 6.—A suspicious case that was under mercurial treatment. Husband had had syphilis. Reaction positive.

CASE 8.—No organic signs of paresis. Progressive mental symptoms. Grandiose delusions with slight alteration of the affective sphere. History of syphilis. Reaction positive.

CASE 21.—Syphilis nineteen years ago. Chancre recently. Suspicion of new infection. Reaction positive.

CASE 24.—Slight intellectual deterioration and paretic speech. No organic changes. Good history. Reaction positive.

CASE 28.—Consultants divided between cerebral syphilis and tubercular meningitis. Reaction positive.

CASE 31.—A well-marked case of pseudoleukemia which gave a positive reaction.

Seven of these patients were from the Woodville County Home

through the kindness of Dr. Srodes, and one from St. Francis Hospital through the kindness of Dr. Hersmann.

The results obtained by those who have examined large numbers of sera are quite uniform, namely, that about 80 per cent. of syphilitic individuals irrespective of the type of syphilis, give a positive reaction, and that the blood of patients who positively have a non-syphilitic disease invariably gives a negative reaction. Citron, for instance, reports on 307 cases; 156 of these were non-syphilitic, and all of the latter gave a negative reaction; 108 were of different types of lues, of which 74 per cent. were positive; 43 cases were of paresis and tabes, of which 79 per cent. were positive. Fleischmann reports 192 cases, 160 of which, or 84 per cent., were positive. Blaschko reports his cases according to the stage, and his positive results were as follows:

90 per cent., initial stage.
98 per cent., first stage.
91 per cent., late stage, without symptoms.
57 per cent., late stage, without symptoms.
60 per cent., cerebrospinal symptoms.

He endeavors to show by this that the reaction is most positive at the time that the syphilis is most florid, and decreases in its positiveness as the clinical evidence of the syphilis diminishes.

Although results differ somewhat, different observers agree in accepting the value of this reaction when positive. When the result is negative, however, it can not be accepted as indicating anything. The fact that the results in tabes and paralytic dementia are so strikingly positive—though these are chronic diseases in which the etiologic factor is one which has been present with the patient for years—indicates very strongly that we must take these diseases from the category of metasyphilitic and parasyphilitic diseases and group them positively as diseases of luetic origin, and more than this, diseases in which there is still an active agent at work.

We can believe this, and still subscribe to the doctrine that this test is a reaction for all protozoan diseases, for there are no other diseases of protozoan origin, as far as we know, that clinically might be confused with diseases which are of luetic origin. It has recently been reported that this reaction is positive in scarlet fever, which would seem to indicate that this is a protozoan disease.

Accepting, therefore, as we must, the reliability of the serum diagnosis of syphilis when the result is positive, its incalculable value, prognostically considered, can readily be seen. Instead of unfortunate individuals being compelled to go through years of their lives not knowing whether they have had, or have not had, syphilis, they can now discover

whether they have been infected with this dreaded disease. And more than this, a physician can ascertain the results of active treatment and inform the patient accordingly. The different sociological questions concerning the marriage of syphilitic patients, their future prospects and their offspring, and the detection of syphilis in wet-nurses, may also be answered by means of further study of this method of diagnosis.

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22. Landsteiner: XIV Internat. Kongress f. Hyg., etc., Berlin, 1907.
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ACUTE INSUFFICIENCY OF THE SUPRARENALS.*

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PHILADELPHIA.

It is interesting that a condition looked on as one of considerable importance by the French clinicians is accorded but the most indifferent consideration by those of other countries. Hemorrhage of the adrenals has been generally recognized as a common pathologic finding in still-born infants or those dying shortly after birth, and the literature of Italy, Germany and England contains occasional references to hemorrhage or other acute destructive lesions of the adrenals in adults. In none of the countries outside of France, however, has acute insufficiency of the adrenals become a factor in medical diagnosis in advanced life as well as in infants. It might be suggested that this state of affairs is but the result of the conservatism of the American, German, English and Italian clinicians contrasted with the somewhat more unstable, fanciful attitude of their French brethren. That a symptom-complex dependent on acute insufficiency of the adrenals does occur, however, in such a striking form as to demand clinical recognition is well exemplified by the case which I have to bring before you.

Patient.—A woman, admitted to the University Hospital, where in the capacity of clinical assistant to Dr. Stengel, I had the opportunity of observing her during her illness and of subsequently performing the postmortem examination. She was a widow, 44 years of age, white, and a native of Ireland. The few elements of her family history that were obtainable had no bearing on her present condition. Her previous history revealed the fact that during the past seven years she had had infrequent attacks of asthma, and that during the past two years she had been subject to occasional attacks of abdominal pain with vomiting. During the past two years she had lost slightly in weight.

History of Illness.—On November 30, shortly after eating breakfast, and while in comparatively good health, the patient had an attack of vomiting, with some pain in the epigastrium, at the same time she felt weak and prostrated. A half hour later she drank a glass of water, when she again vomited. The pain in the epigastrium became more severe and the attacks of vomiting more frequent. During the afternoon there were frequent attacks of vomiting, and toward the evening the patient became slightly delirious. She was then seen by Dr. H. Kennedy Hill, who immediately sent her to the University Hospital. On admission to the hospital, temperature was 95, respiration 48, and no pulse could be felt. Vomiting had ceased by this time. The patient complained of pain in the epigastrium, and there was tenderness in this region and in the loins. The predominating symptoms were those of shock; the patient was extremely apa-

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thetic; her extremities were cold, the skin leaky and absolutely no radial pulse could be felt. During the earlier part of the next day the breathing became of the Cheyne-Stokes type.

Physical Examination.—The lungs were slightly emphysematous, and on respiration numerous dry râles could be heard. The upper border of the heart was on a level with the fourth rib; the right border at the right border of the sternum; the left border about a quarter of an inch outside of the left midclavicular line; the apex-beat was in the fifth interspace in the midclavicular; the cardiac sounds were weak and somewhat obscured by the respiratory râles; no murmurs could be detected. The tenderness in the epigastrium and in the loins persisted. There was slight rigidity of the abdominal wall, but no distention. The extremities were cold and slightly cyanosed.

Urinalysis.—Straw colored; slight brownish sediment; acid; specific gravity, 1002; no sugar or albumin; a small amount of mucus; a few leucocytes.

Blood Examination.—Hemoglobin, 61 per cent.; erythrocytes, 4,930,000; leucocytes, 52,800.

Clinical Course.—With vigorous stimulation during the day after admission, the patient reacted slightly, her temperature becoming 100 at noon on the day following admission. This reaction lasted for but a short time, the patient dying at 8 o'clock in the evening following her admission, or about thirty-six hours after the onset of the illness. Respiration had remained in the neighborhood of 48; the radial pulse had at no time become palpable. As counted by auscultation, the heart beat from 120 to 140 times per minute.

It is almost needless to emphasize how impressive a clinical picture the patient presented—the suddenness of onset, the vomiting, the epigastric pain, the lumbar tenderness, and, above all, the profound shock formed a most striking group of symptoms. In the light of our knowledge at the time, it resembled most acute hemorrhagic pancreatitis, though the shock was more profound and the vomiting and epigastric tenderness less marked than would have been expected in this condition.

The autopsy revealed the interesting and unexpected nature of the affection. The following brief notes are abstracted:

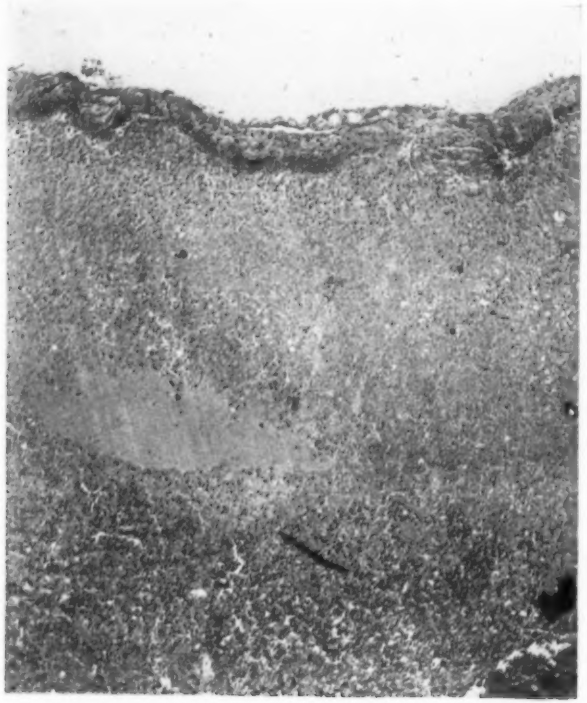
Pathologic Report.—The lungs showed, macroscopically and microscopically, a moderate degree of emphysema with slight hypostatic congestion. The heart was of normal size; both ventricles were relaxed; the cavities and walls were of normal proportions; the valves were soft and competent; the coronary arteries were slightly sclerotic; the muscle was somewhat grayer than normal. Microscopically, the heart muscle presented the picture of a slight, chronic fibrous myocarditis. The peritoneum was smooth and glistening. The uterus and appendages, aside from slight atrophy, presented no pathologic features. The kidneys were of normal size; their consistency considerably increased; the capsule stripped with some difficulty, but did not tear the kidney substance; the surface was slightly granular and showed a number of dark-based depressions and a few small cysts containing clear fluid. The microscopic features were characteristic of an arteriosclerotic, chronic interstitial nephritis of moderate degree. The stomach showed itself to be the seat of a chronic catarrhal gastritis. The intestines were without noteworthy characteristics, except for considerable venous congestion. The spleen was slightly enlarged and softer than normal. The liver was of normal size, its consistency slightly reduced; the organ was paler than normal, its structure somewhat obscured. The microscopic examination revealed fatty degeneration with early periportal fibrosis. The bile ducts were patulous; there

were no gallstones. The pancreas was of normal size, the consistency increased, the structure somewhat obscured; on squeezing the organ, a few droplets of turbid, yellowish fluid were expressed from the smaller ducts; several pinhead-sized areas of fat necrosis were found in the peri-pancreatic fat. Microscopically, a distinct interlobular and intralobular fibrosis was seen, with some atrophy of the secreting cells; there was no necrosis; in the interlobular tissue, especially in the neighborhood of the ducts, there was a diffuse, polynuclear leucocytic infiltration of moderate degree. Both suprarenals were enlarged and soft, and presented on section a dark-red, homogeneous appearance; both suprarenal veins were thrombosed. Microscopically, there was almost complete destruction of the gland substance; with the exception of small, scatttered islands, the parenchyma of the cortex stained a homogeneous pink with hematoxylin and eosin. Nuclei of the connective tissue cells of the stroma were preserved here and there, but scarcely any epithelial nuclei were visible. Scattered throughout this necrotic tissue were hemorrhagic extravasations of various size. There was considerable hemorrhage into the medulla, but less cellular and nuclear destruction than in the cortex. Cultures from the pancreas showed staphylococci, colon bacilli, and a non-identified Gram-positive bacillus. Cultures from the suprarenals were negative.

Pathologic Diagnosis.—Emphysema and hypostatic congestion of the lungs; chronic fibrous myocarditis, chronic interstitial nephritis; chronic catarrhal gastritis; acute splenic tumor; fatty degeneration of the liver, with beginning periportal cirrhosis; chronic pancreatitis, with acute interlobular suppurative pancreatitis; thrombosis of the suprarenal veins and acute hemorrhagic necrosis of the suprarenals.

My interpretation of these pathologic findings in their relation to the clinical phenomena is that the woman had a chronic pancreatitis of probably some years duration. Recently an acute suppurative inflammation was engrafted on this, the suprarenal veins became thrombosed as a result of this neighboring inflammation, and the hemorrhagic necrosis of the suprarenals resulted. The remaining pathologic features were for the most part the result of the existing arteriosclerosis.

Almost the only two conditions characterized by insufficiency of the suprarenals are hemorrhage and so-called adrenalitis. These two can be neither clinically or pathologically well differentiated in most cases. Adrenalitis is in the vast majority of cases not a true inflammation, as the term would imply, but a necrotic process, with which more or less hemorrhagic extravasation is always associated. When both necrosis and hemorrhage are present the two are generally the common results of the same condition, a vascular thrombosis. On the other hand, a number of the cases do present the clinical and pathologic features characteristic of simple hemorrhage. Many of these cases, by reason of the suddenness of the insult and the frankness of the hemorrhage, are appropriately termed adrenal apoplexies. The relation of suprarenal hemorrhage to acute hemorrhagic adrenalitis may be perhaps better understood by calling attention to the analogy that at least pathologically exists



Lumière photomicrograph of necrotic suprarenal. Section stained with hematoxylin and eosin.

Lumière photomicrograph of normal suprarenal. Section stained with hematoxylin and eosin.

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between them and pancreatic hemorrhage and acute hemorrhagic pancreatitis.

I have been able to find but two cases in which insufficiency of the adrenals was dependent on other pathologic lesions than hemorrhage or necrosis. One is the case of Janowski,[1] in which the two adrenals formed small abscesses above the two kidneys. The other is the case of Stursberg,[2] in which suppuration was found in both suprarenals of a woman suffering from Pott's disease. It is not improbable that the glands in this case were tuberculous.

Confining our attention then to necrosis and hemorrhage, let us determine what the factors are bearing on these two conditions. The extraordinarily rich vascularization of the organs naturally impresses itself as standing in some relation to the frequency of hemorrhage. The gland receives its blood supply from three sources, the aorta, the renal artery, and the arteries of the diaphragm. The arterioles and the capillaries from these sources form a dense network about the cells of the cortex, and the capillaries and venules finally unite in the inner cortical layers and medulla to form a single vein, which emerges at the hilus of the organ. The facts that such a large amount of blood unites to enter one vessel in the medulla, and that extensive hemorrhages usually seem to occur into the medulla, suggest that simple alterations in the blood supply or blood pressure of the organ may be the determining factors in the production of the hemorrhage. This hypothesis has been put forth as especially applicable to hemorrhage of the adrenals so frequently found in the new-born. The great increase in intra-abdominal pressure in the child, incident to the uterine contractions, and especially the pressure of the liver on the vena cava just above the suprarenals, have both been thought to be the direct cause of increasing the adrenal blood pressure sufficiently to induce hemorrhage. This view receives some support from the fact that when hemorrhage has occurred into only one of the suprarenals, it has been more frequently on the right than on the left (according to Hamill,[3] fifteen times in twenty-four cases), and the right vein enters the vena cava directly, while the left enters it through the renal vein. These relations would naturally subject the vessels of the right gland to greater pressure than the left in the presence of any cause obstructing the return of venous blood.

Chronic heart disease associated with passive congestion has been observed in a number of cases, and has thus been looked on as a causal factor.

1. Janowski: Gaz. lek., 1898, liv, 354.
2. Stursberg: Deutsch. med. Wchnschr., 1904, xxx, 1406.
3. Hamill: Arch. Pediat., 1901, xviii, 161.

Similarly, chronic pulmonary disease has been not infrequently found in these cases, and it is possible that the chronic passive congestion resulting therefrom has been an active factor in the production of hemorrhage.

A certain number of cases have been observed in which death has resulted after the occurrence of phenomena tending to a great increase in blood pressure, and in which, at autopsy, hemorrhage of the suprarenals was found. A striking example of this is a case reported by Ogle[4] of an epileptic dying after two weeks of almost continuous convulsions. At the autopsy hemorrhage into both suprarenals was discovered. I believe that it is not improbable that in some of the cases said to have manifested themselves clinically by convulsions these were the cause rather than the result of the hemorrhage, induced by the great increase in blood pressure incident to the convulsions. Duckworth[5] refers to a case in which the paroxysms of coughing in a child with pertussis apparently induced hemorrhages into both adrenals.

The great tendency to hemorrhage throughout the body in asphyxia, in all probability as the result of venous engorgement, has caused it to be looked on as one of the possible factors in the production of suprarenal hemorrhages, especially in the new-born. A factor emphasized by Spencer[6] as responsible for the greater frequency of suprarenal hemorrhages in infancy is the normal delicacy of the blood-vessel walls in this period of life.

Thus far we have dealt with only passive congestions. It has been asserted that active congestion also plays a rôle in the production of adrenal hemorrhage. One of the functions attributed to the suprarenal capsule is that of neutralizing toxins, and it is said that the functional activity of the gland in the presence of a toxic agent in the body so increases its blood supply as to lead to hemorrhage.

It is doubtful, however, if it is alone by increasing the blood supply to the gland that infections and intoxications act in inducing insufficiency of the suprarenals. In a number of cases organisms have been isolated directly from the adrenal glands, the seat of hemorrhage and necrosis. Klebs and Eppinger[7] isolated an organism in several cases of suprarenal hemorrhage in the new-born, which they called *Mona hemorrhagica*. Gaertner[8] isolated a bacillus resembling the colon bacillus, and

4. Ogle: Tr. Path. Soc., London, 1863, xiv, 127.
5. Duckworth: Twentieth Century Practice of Medicine, ii.
6. Spencer: Tr. Obst. Soc., Lond., 1891, xxxiii, 203.
7. Klebs and Eppinger: Boston Med. and Surg. Jour., 1891.
8. Gaertner: Arch. f. Kinderh., 1895.

Riesman[9] the *Staphylococcus albus* and *aureus* from four out of six cases occurring within a short space of time.

Experimentally, hemorrhage and acute destructive lesions of the glands have been produced by Roux and Yersin[10] by inoculating rabbits and guinea-pigs with diphtheria bacilli; by Charrin and Langlois[11] with the *Bacillus pyocyaneus;* and by Roger[12] with the bacillus of Friedlander. Pettit,[13] Pilliet[14] and Wibaud[15] have confirmed these results. Oppenheim and Loeper[16] have produced similar results by injecting the toxins of Friedlander's bacillus, of the diphtheria bacillus and the tetanus bacillus, as well as by arsenic, phosphorus and mercury. Practically the same results were obtained by Bernard and Bigart[17] in injecting various metallic poisons.

Adrenal hemorrhage associated with a general purpuric eruption can be looked on only as a visceral manifestation of a general hemorrhage tendency. As the purpuras of childhood are practically always infectious, the functional activity of the gland as the result of the infection, according to the above-mentioned hypothesis, probably increases its predisposition as a seat of hemorrhage.

Trauma does not seem to play a very important rôle in the production of acute destructive suprarenal lesions. In but two cases, those of Canton[18] and Mattei,[19] does trauma seem to have been the cause of the adrenal hemorrhage found subsequently at autopsy. The secluded, well-protected position of the adrenals is probably the cause of its being so infrequently affected by trauma.

In the cases of Arnaud,[20] Churton[21] and Dudgeon[22] adrenal hemorrhage was apparently induced by severe surface burns. In Dudgeon's and Arnaud's cases there were symptoms of adrenal insufficiency before death. This association suggests that which exists between surface burns

9. Riesman, quoted by Hamill: Arch. Pediat., 1901, xviii, 161.
10. Roux and Yersin: Ann. de l'Inst. Pasteur, 1889.
11. Charrin and Langlois: Compt. rend. Soc. biol., 1896, Series 10, iii.
12. Roger: Presse méd., 1894, i, 35.
13. Pettit: Thèse de Paris, 1896.
14. Pilliet: Arch. de physiol. norm. et path., Series 5, F. 7.
15. Wibaud: Etude des capsules surrénales dans les maladies infectieuses expérimentales, Brussels, 1897.
16. Oppenheim and Loeper: Arch. de méd. expér., 1901, xiii, 332.
17. Bernard and Bigart: Jour. de physiol. et de path. gén., 1902, iv, 1014.
18. Canton: Tr. Path. Soc. Lond., 1863, xiv, 257.
19. Mattei: (Case 2) Sperimentale, 1883, li, 386.
20. Arnaud: (Case 1) Arch. gén. de méd., 1900, clxxxvi.
21. Churton: Lancet, London, 1886, i, 245.
22. Dudgeon: (Case 2) Am. Jour. Med. Sc., 1904, cxxvii, 134.

and duodenal ulcer. Whether the adrenal lesion results from internal congestion, toxic products or embolism is quite as much open to question as the pathogenesis of duodenal ulcer.

Suppurative inflammations of adjacent organs has apparently been the cause of necrosis and hemorrhage of the suprarenals, with the clinical signs of insufficiency in three cases—my own and two of Arnaud's.[23] In one of Arnaud's cases the neighboring lesion was an abscess of the liver, in the other a suppurating hydatid cyst of the liver. In all three cases thrombosis of the adrenal veins was apparently the immediate cause of the changes in the glands. It is possible that pneumonia acts in the same way in producing acute insufficiency of the adrenals as to these lesions of neighboring abdominal viscera.

The appearance of the gland varies with the nature and extent of the lesion. Simple hemorrhages usually occur into the medulla of the organ. If of small size the hemorrhage merely distends the cortex slightly, producing but little destruction of its cellular elements. If of larger size it may so distend the organ that the cortex forms but a thin shell enclosing a large blood cyst. Rayer[24] records a case in which hemorrhage into a suprarenal gland resulted in a blood cyst weighing two kilos. Carrington[25] reports a case in which the suprarenals were transformed into cysts the size of large oranges, and in Routier's[26] case 1,600 cubic centimeters of a blackish-brown fluid were evacuated from a suprarenal, the seat of hemorrhage. At times the capsule of the gland ruptures, permitting the escape of blood either into the surrounding retroperitoneal tissues or into the peritoneal cavity itself.

When hemorrhages are multiple and small they are usually found in the cortex rather than in the medulla. In such cases more or less necrosis of the epithelial elements of the cortex is usually present. The necrosis and hemorrhage may be the common result of the same cause, thrombosis, or the necrosis may be either the cause or the result of the hemorrhage. Judging from the pathologic features of my case, venous thrombosis results in extensive necrosis with but slight hemorrhage. In such cases the gland presents macroscopically a homogeneous, reddish-brown appearance and a microscopic picture similar to that described in the above pathologic notes of my case.

The fact that the lesions are at times limited more or less to either cortex or medulla has led to an attempt to classify the symptomatology

23. Arnaud: (Cases 2 and 3) Arch. gén. de méd., 1900, clxxxvi, 5.
24. Rayer: (Case 1) Journal de l'expérience, 1837.
25. Carrington: Tr. Path. Soc., London, 1885, xxxvi, 454.
26. Routier: Bull. Soc. d'anat. de Paris, 1895, 73.

according to the involvement of one or the other of these parts. Experimental evidence indicates that the functions of the cortex and medulla are different. The medulla seems to supply the elements having to do especially with the preservation of vascular tone, while the function of the cortex, aside probably from acting to an extent in a compensatory way for the medulla, appears to be the furnishing of an antitoxic agent to the body. In the majority of the cases of sudden death in adrenal insufficiency the hemorrhage does seem to have occurred into the medulla, but we are hardly justified in deducing from this fact the conclusion that this result attends destruction of only this portion of the gland. The functions of the adrenals are as yet too little understood and the limitations of the pathologic lesions involving them too poorly defined to warrant more than the statement that insults to the glands, regardless of their location or extent, may call forth certain profound symptoms such as will be described in the clinical discussion.

A study of the literature reveals a number of apparently incongruous relations requiring discussion. Numerous cases have been observed presenting the symptoms of acute suprarenal insufficiency in which only one of the glands was involved, the other being apparently normal. Why the compensatory action of the normal gland should not be capable of abolishing these symptoms is beyond the limitations of our pathologic knowledge to say. It is not improbable that our means of study are incapable of discovering lesions which, without destroying the morphologic integrity of the apparently normal organ, yet seriously interfere with its functions. A number of cases (those of Addison,[27] Goolden,[28] Carrington,[25] Greenhow,[29] and Mattei[30]) have been reported in which the symptoms of Addison's disease were presented and in which at autopsy acute adrenal lesions were found. In all of them the diagnosis of Addison's disease, as judged by the reported symptoms, is open to doubt, but even were it authentic it is rational to consider that a chronic degenerative process would only predispose the gland to hemorrhage or other acute process which by its prominence could obscure the recognition of the chronic changes. An interesting group of cases is that in which the signs of acute suprarenal insufficiency occur, followed shortly by death, and at autopsy the destructive lesions of a chronic process are found in the suprarenals.

27. Addison: On the Constitutional and Local Effects of Disease of the Suprarenal Bodies (Case 10), London, 1855.
28. Goolden: Lancet, London, 1857, ii, 266.
29. Greenhow: Lancet, London, 1877, i, 349.
30. Mattei: (Case 3) Sperimentale, 1883, li, 386.

In regard to such cases it must be emphasized that the degree of tissue destruction is not always a measure of functional incapacity, and it is very possible that only when the destructive process has reached a certain degree, or involved certain elements, does it manifest itself clinically.

Since, as above stated, hemorrhage of the suprarenals and acute hemorrhagic adrenalitis can not be strictly differentiated either clinically or pathologically in the majority of cases, I shall not employ these two conditions as a basis for classification. The symptoms presented result from interference with the function of the adrenals, regardless of the agent inducing it. Even on the basis of the clinical phenomena I hesitate to attempt a classification for fear of confusing the reader in a maze of artificial grouping, for few of the cases conform to one type entirely distinct from the others. However, on the basis of the preponderance of one or another group of symptoms, I think that the following classification will serve as a basis for clinical consideration.

1. Cases of sudden onset with epigastric pain and tenderness, vomiting, profound prostration, feebleness and rapidity of pulse, coldness of extremities, lumbar tenderness, and at times diarrhea, and abdominal distention, followed within a few days by death. This is the symptom-complex that at times is called the peritoneal type of acute insufficiency of the adrenals, of which my case is a striking example. The literature of the subject contains a number of similar instances, among the most impressive of which are those of Stursberg,[2] Pritchard,[31] Mattei,[32] Arnaud,[33] Janowski[1] and Sotti.[34] The occurrence of the same group of symptoms in children is well exemplified by such cases as those of Batten,[35] Dudgeon,[22] and the two cases of Talbot.[36] There is a striking resemblance between the cases of this type and many cases of acute hemorrhagic pancreatitis. Judging from the one case that I have observed, the shock is more profound, the lumbar tenderness more acute, and the epigastric pain and vomiting less pronounced in adrenalitis than is usually the case in acute hemorrhagic pancreatitis.

2. The asthenic type, in which the predominant feature is a profound asthenia ending within a few days in death. Instances of this

31. Pritchard: Lancet, London, 1890, i, 750.
32. Mattei: Sperimentale, 1863, ii, 3.
33. Arnaud: (Case 1) Arch. gén. de méd., 1900, clxxxvi, 5.
34. Sotti: Policlinico, 1908, xv; Sem. méd., 1.
35. Batten: Tr. Path. Soc., London, 1893, xliv.
36. Talbot: St. Barth. Hosp. Rep., 1900, xxxvi, 207.

type have been reported by Greenhow,[29] Murray,[37] Sicard[38] and Voisin and Norero,[39] all occurring in adults. In Sicard's case the asthenia was so pronounced as to give the case the appearance of an acute bulbo-spinal myasthenia. Interesting cases resembling those included in this group, except for their duration, are those reported by Marchand,[40] and Bernard and Heitz.[41] In Marchand's case the duration was three months, in Bernard and Heitz's case five months. In both of them there was an extreme degree of asthenia, and at autopsy simple atrophy of the adrenals was found in both cases. Bernard and Heitz employ their case to justify them in originating a condition which they term subacute insufficiency of the suprarenals.

3. The nervous type, in which the predominant symptoms have been either convulsions, as in the cases of Portal,[42] Valleix,[43] Parrot[44] and Droubaix;[45] or coma, as in the cases of Arnaud,[46] and Laignel-Lavastine;[47] or delirium, as in the cases of Mattei[48] and Ribadeau-Dumas and Bing;[49] or a typhoid state, as in the cases of Virchow[50] and Kohler.[51] These varied symptoms have been noted in children, as well as in adults. In some of the cases in which convulsions have been a predominant feature I think it not improbable, as mentioned above, that they were the cause rather than the result of the injury to the adrenals.

4. Cases of sudden death. In this group I include the cases of sudden death in which at autopsy nothing except a destructive lesion of the adrenals, usually hemorrhage, has been found. It may be thought presumptuous in such cases to conclude that the sudden death was due to the adrenal lesion, but realizing from experimental evidence and from the clinical evidence of the more protracted cases how profound an influence destruction or injury of the suprarenals has on life, I think that it

37. Murray: Tr. Path. Soc., London, 1870, xxi, 395.
38. Sicard: Bull. Soc. méd. d'hôp. de Paris, 1904, xxi, 848.
39. Voisin and Norero: Bull. Soc. d'anat. de Paris, 1906, lxxxi, 320.
40. Marchand: Deutsch med. Wchnschr., 1903, xxix.
41. Bernard and Heitz: Tribune méd., 1904, New Series ii, 325.
42. Portal, quoted by Lieutaud: Historia anatomica, 1769, i, 285.
43. Valleix: Clinique des maladies des enfants nouveau-nés (Case 22), Paris, 1838.
44. Parrot: (Cases 10 and 11) Arch. gén. de méd., 1872, xix, 257.
45. Droubaix: Thèse de Paris (Case 1), 1887.
46. Arnaud: (Case 4) Arch. gén. de méd., 1900, clxxxvi, 5.
47. Laignel-Lavastine: Bull. Soc. anat. de Paris, 1902, lxxvii.
48. Mattei: (Case 1) Sperimentale, 1883, li, 386.
49. Ribadeau-Dumas and Bing: (Case 2) Bull. Soc. anat. de Paris, 1904, lxxix, 477.
50. Virchow, quoted by Lancereaux: Dict. encycl. d. sc. méd., 1875, iii, 155.
51. Kohler: Dict. encycl. d. sc. méd., 1875, iii, 155.

is a justifiable inference. This I believe to be true of still-born infants in whom this lesion is found, as well as in cases of advanced life. Instances of this type have been reported by Rayer[52] and Goodhart,[53] and Hamill[3] has collected the cases occurring in still-born infants and children reported up to the year 1900.

5. Cases occurring in association with a purpuric eruption or hemorrhages into the abdominal viscera. Numerous cases of this type occurring in children are reported in the literature. I have been able to find none occurring in adults. Undoubtedly the hemorrhage into the suprarenals in these cases is but a manifestation of the general hemorrhage tendency as a result either of infection, or, in some cases, possibly of asphyxia. The English clinicians have been inclined to look on these cases as possible instances of hemorrhagic smallpox, especially by reason of the fact that many of the affected children have been unvaccinated. As there is little else than this one fact in support of their view, I think it can not be looked on as a probable one.

Though the majority of cases permit themselves to be classified in one or another of the above groups, many are characterized by symptoms common to more than one group. The cases in which purpura is a prominent feature may present symptoms characteristic of the peritoneal or nervous type, and cases of the asthenic or nervous type may in addition present some symptoms belonging to the peritoneal type. Of all the symptoms the most constant and one of the most characteristic is a greater or less degree of asthenia. The occasional occurrence of two other symptoms is worthy of mention. They are tumor and the *ligne blanche* of Sergent.[54] A tumor, the result of suprarenal hemorrhage, is mentioned as having been determined during life in three instances. In one of Rayer's[24] cases it involved the right suprarenal and presented itself in the epigastrium. In Routier's[26] case a hemorrhage into the left suprarenal formed a palpable tumor in the left hypochondrium. In Leconte's[55] case there was a fluctuating tumor on each side of the mid-line extending from the hypochondrium to the iliac fossa. The *ligne blanche,* or white lines produced by stroking the skin with the finger, are looked on by Sergent as being of great diagnostic value in suprarenal insufficiency. They result from the temporary constriction of the relaxed vessels. As the majority of observers agree that they can be produced in various conditions attended by vasomotor relaxation, I can not agree with Ser-

52. Rayer, quoted by Roger: Jour. de l'expérience, 1837.
53. Goodhart: New Sydenham Society's Atlas of Pathology, 1879, ii, 50.
54. Sergent: Bull. Soc. méd. d'hôp. de Paris, 1904, xxi, 380.
55. Leconte: Thèse de Paris (Case 48), 1897.

gent in looking on them as diagnostic of adrenal insufficiency. As clinical investigation has as yet advanced no pathognomonic signs of the condition, it is only when the symptoms observe a sufficiently characteristic grouping that the possibility of diagnosis during life can be entertained. Attention should be paid to the relative frequency of the condition in the purpuras of childhood and during or shortly after the acute infections. An interesting case occurring subsequent to an acute infection is that reported by Sicard of a woman 33 years of age, who shortly after the crisis in Friedlander's pneumonia suddenly manifested a most profound asthenia; death occurred within a few days, and at autopsy hemorrhage and necrosis of both adrenals was found. Bousset[56] asserts that he has recognized acute insufficiency of the suprarenals as indicated by asthenia, arterial hypotension, nausea, vomiting and diarrhea eight times in the course of various acute infections and that he has caused their subsidence by hypodermic injections of adrenalin. Due consideration must be paid to the apparent etiologic relationship that exists between acute suprarenal insufficiency and inflammations in the neighborhood of the suprarenals, surface burns, chronic heart or pulmonary disease, and any phenomenon tending to a great increase in internal blood pressure.

Such cases as those of Laignel-Lavastine and Arnaud claim for acute suprarenal insufficiency a rôle of some importance as a possible factor in apoplectiform deaths. Both of the patients were men, respectively 36 and 47 years of age, apparently previously in good health, who suddenly fell unconscious and died in coma, one twelve hours, the other forty-eight hours after the onset. At autopsy the only finding of note was hemorrhage into the suprarenals. When physiology has taught us more of the functions of the suprarenals, and when they are subjected to a more rigid routine postmortem examination, and when clinicians pay more attention to the facts already determined, I have no doubt that acute suprarenal insufficiency will assume a position of greater clinical importance than it has maintained in the past.

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56. Bossuet: Gaz. hebd. de méd. de Bordeaux, 1904, xix.

THE COMPARATIVE MORPHOLOGY OF THE SPIROCHETES OF SYPHILIS AND YAWS (FRAMBŒSIA TROPICA).*

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There has always been considerable interest in the tropical disease known as yaws or frambœsia tropica, not only for itself, but also on account of its resemblance to syphilis, and one group of English physicians, headed by Mr. Hutchinson,[1] has even gone so far as to say that if "yaws be not syphilis it is very clear that it offers a very exact parallel to it." The physicians of Mr. Hutchinson's school have tried to clear up the question of the origin of syphilis by suggesting that it is an evolutionary form of yaw.[2] All authorities unite in agreeing that the two diseases have many points of resemblance and that their relationship to one another is a most intimate one.

When the spirochete of yaws was first described by Castellani[3] in June, 1905, his announcement aroused great interest among the students of syphilis as well as among the students of tropical diseases. It seemed probable that at least one of the riddles of medicine might now be answered.

In his first publication[3] Castellani says distinctly that he does not commit himself in any way as regards the etiology of Parangi. In his second article on the subject[4] he is still non-committal. In his third report,[5] which was published only one week later, he tells us that Professor Schaudinn had kindly examined some of his preparations and had written him under date of Aug. 8, 1905, that the yaws smears contained three varieties of spirochetes, one of which was very delicate and resembled closely *Spirochæta pallida,* and at this time Castellani expresses himself very decidedly as to the identity of the two organisms. In his summary he says that one of these spirochetes is extremely delicate and, in his opinion, it is absolutely identical with *Spirochæta pallida* of

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* Read at the fifth annual meeting of the American Society of Tropical Medicine, held in Baltimore, March 28, 1908.

1. Allbutt and Rolleston: System of Medicine, Lond., 1907, ii, Part ii, 701.
2. Osler: Modern Medicine, Phil., 1908, iii, 439.
3. Castellani, Aldo: Jour. Ceylon Br. Brit. Med. Assn., 1905, ii, 54.
4. Castellani, A.: Brit. Med. Jour., Nov. 11, 1905, ii, 1280.
5. Castellani, A.: Brit. Med. Jour., Nov. 18, 1905, ii, 1330.

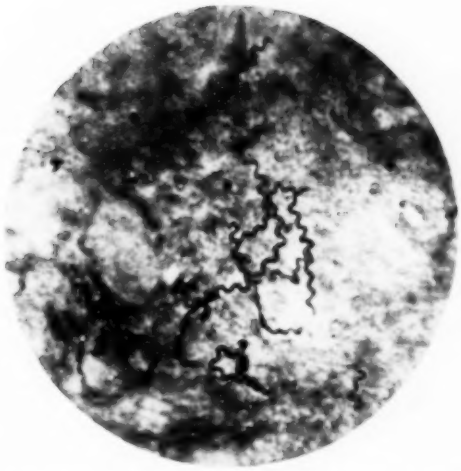

Fig. 1.—Spirochete of yaws, *Spirochæta pertenuis* (×1500).

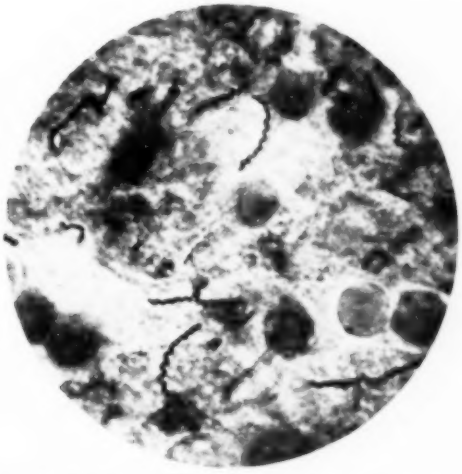

Fig. 2.—Spirochete of syphilis, *Spirochæta pallida* (×1500).

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Illustrating Article by Frederick F. Russell, M.D.

Schaudinn. But even after making such a positive statement as that he has apparently not convinced himself in the matter, as he adds in the same breath that "if my hypothesis should be proved to be wrong a proper name for the organism might be *Sp. pallidula*. Castellani's next article[6] is entitled "Is Yaws Syphilis?" This is not a mere note on the question, but a rather complete discussion of the entire problem, and in this paper he comes to two conclusions which at first sight are not consistent with one another. He concludes that yaws is not syphilis, and also that spirochetes of yaws are, in his opinion, morphologically identical with *Spirochæta pallida* of Schaudinn; he maintains, however, that this does not prove the identity of the two diseases, since the bacillus of leprosy and of tuberculosis and many other acid-fast bacilli are morphologically identical while the diseases are quite distinct.

Since 1906 three independent series of studies have been made on the subject of the unity or duality of syphilis and yaws, and the same general conclusions have been reached in all three studies (Castellani,[7] Ashburn and Craig,[8] L. Halberstaedter[9]), namely, that yaws is a separate and distinct disease from syphilis, and that an inoculation of monkeys with yaws does not confer any immunity against syphilis, nor does the inoculation of syphilis confer any immunity against yaws.

To return now to the question of the morphology of the spirochetes of these two diseases: Last summer I examined numerous smears made from yaw lesions, and I must confess that I could not satisfactorily differentiate one variety from the other, although I felt that there were certain minute differences which are too elusive, however, to be put down in so many words. Later in the year I was so fortunate as to obtain two nodules which had been excised from patients suffering with yaws; these I studied according to the silver nitrate method of Levaditi,[10] and in both specimens were found innumerable spirochetes which at first sight appeared to be absolutely identical with *Spirochæta pallida*. A little study, however, showed that there were differences between the two and that these variations were not accidental, but regular and constant. These differences may be appreciated by comparing the two accompanying photomicrographs, which were taken under exactly the same conditions as to magnification, light, etc. The photomicro-

6. Castellani, A.: Jour. Trop. Med., 1906, ix, 4.
7. Castellani, A.: Jour. Hyg., 1907, vii, 558.
8. Ashburn and Craig: Philippine Jour. of Sci., Manila, 1907, ii, 441.
9. Arb. a. d. k.: Gsndhtsamte, Berlin, 1907, xxvi, 48.
10. Jour. Am. Med. Assn., 1907, xlviii, 605.

graphs represent average fields; they were not selected for this special purpose.

It is evident: (1) That *Spirochæta pertenuis* (Fig. 1) is slightly thicker than *Spirochæta pallida* (Fig. 2).

(2) That the distance from crest to crest of the waves is greater.

(3) That the dip from the crest to the hollow is greater as a rule.

(4) That the waves are not quite so regular in their height.

(5) That the number of forms showing longitudinal division is greater.

(6) That there is a greater tendency for the spirochete to curl up one end into a loop or more or less solid ball.

Prowazek,[11] in some comparative studies on spirochetes, has come to practically the same conclusions as these. He adds one point which is of considerable interest—a point which was forecasted by Castellani in one of his earliest papers—and that is, that these organisms have a resting form which is oval or round and which is produced by a coiling up of the spiral. One often sees individuals with one end looped or coiled into a more or less solid round or oval body which represents a transition stage between the fully extended and the coiled up resting stage.

U. S. War Department.

11. Arb. a. d. k.: Gsndhtsamte, Berlin, 1907, xxvi, 23.

THE THEORY OF CHEMICAL CORRELATION AS APPLIED TO THE PATHOLOGY OF THE KIDNEY.*

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There is perhaps no problem in medicine of greater interest to clinician and pathologist alike than that of the relation which some of the more important manifestations of chronic nephritis, as vascular hypertension, heart hypertrophy, uremia and edema, bear to the renal lesion itself. During the past summer, having in view an experimental study of some phases of vascular hypertension, I undertook a critical review of the general literature of renal physiology and pathology, and was amazed, not only at the multiplicity of theories concerning the relation of the kidney to heart hypertrophy and hypertension, but also at the importance attached by many writers to the part played by the hypothetical internal secretion of the kidney. I use the term "hypothetical" advisedly, for, although certain clinical observations are very suggestive, the experimental basis on which the theory rests appeared to me to be most unstable. Further study of the subject, however, led to the conclusion that the theory, despite conflicting observations, offered, in view of our newer theories of chemical correlation, much that was suggestive and indeed, if established by proper experimental evidence, of fundamental importance in the pathology of the kidney. At the same time I felt that if it were not capable of proof it should be discarded as a hindrance to more profitable study along other lines.

For these reasons I have for the past six months devoted my time entirely to various phases of this problem and have attempted to determine also the effect of products retained in, or arising within, the organism during nephritis and of the correlation of disease of the kidney with the internal secretion of other organs, or, for example, the adrenal; in short, a study of chemical correlation in its broadest sense, as applied to the kidney. It is the results of this study which I now present. Such an investigation, as it naturally includes to a considerable extent a repetition of the experiments of others and as its scope is somewhat comprehensive, is as yet far from complete. It has advanced sufficiently, however, along all lines to allow me to give you a more or less satisfactory summary of my results.

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*Annual address before the Philadelphia Pathological Society, April 23, 1908.

I wish at the outset to have it clearly understood that I use the term "chemical correlation" in the broadest possible sense to include the action on any organ or tissue, or group of organs or tissues, of any substance or substances present in the blood as the result of the normal or abnormal life processes of any other organ or tissue. My discussion must, therefore, include the older theory of internal secretion with its newer aspect, the action of hormones, as well as the action of products of metabolism. I do not think it necessary to explain these theories. As examples of these types respectively it is sufficient to mention the secretion of the adrenal, the action of secretin, and the influence of carbon dioxid on the respiratory center.

The knowledge derived from these various phases of chemical correlation will be applied to the pathology of the kidney in an attempt to explain, or at least to offer a working basis for the understanding of, the increased blood pressure, the uremia, the edema and the disturbance of metabolism associated with chronic renal disease. And although I have been unable to reach definite conclusions in regard to all these matters, I think that a presentation from this point of view may perhaps be suggestive and an incentive to discussion.

With this explanation let me glance for a moment at the older observations on which the theory of internal secretion, as applied to the kidney, is based. The subject was first brought to general notice by Brown-Séquard, who, as the result of his investigation of the internal secretion of the testicle, came to very broad conclusions concerning internal secretions in general, and stated that the kidneys, as also other organs, have this function. He based his opinion as regards the kidney on clinical observation and the study of dogs from which both kidneys had been removed as compared with those in which the ureters had been ligated. As the result of such procedure the retention of metabolites is the same; but in the nephrectomized animals death, which comes on more rapidly, is supposed to be due to the absence of an internal secretion which, it is assumed, is still furnished by the ligated kidneys. If, he maintained, in the nephrectomized animals the internal secretion is replaced by the injection of renal juice, or glycerin extracts of kidney or by normal serum, the animals live as long or even longer than those which have had both ureters ligated. Such observations are urged in support of the theory of internal secretion by those who do not believe uremia to be due to retention of the products of metabolism.

Bradford's extirpation experiments, characterized by a marked wasting of the body, polyuria and increased loss of nitrogen, with especially an increased elimination of urea, are also offered in support of this

theory, although Bradford states definitely that he made no observations which indicated that these changes were due to the disturbance of an internal secretion.

Similarly, metabolism experiments on man which tend to show that uremia may occur without evident nitrogen retention are viewed in the same way and are taken by those who support the theory of internal secretion to indicate that uremia is not due to lack of elimination of metabolites but to loss of the internal secretion.

Analogous to the injection of kidney extracts into nephrectomized animals are the attempts at organotherapy—the feeding of kidney extracts to nephritics with or without uremia—having for their object the replenishment of the internal secretion which the diseased kidney fails to furnish.

As regards the effect of the kidney on blood pressure, Tigerstedt and Bergman found that extracts of the kidney substance of the rabbit prepared in various ways caused a rise in pressure when injected into the rabbit. These experiments are frequently quoted in the discussion of the hypertension of contracted kidney as evidence of the effect of an internal secretion on the vascular system. To these older views may be added more recent observations, such as those which assume a correlation between the adrenal and the kidney of chronic interstitial nephritis in the production of arteriosclerosis and the question of the development of endotheliotoxic and nephrotoxic substances during nephritis. All these observations, which must be considered in connection with the theories of internal secretion and chemical correlation, may be grouped for purposes of discussion under the following headings:

1. Clinical observation of the effects of nephrectomy and ligation of the ureter in man.

2. Experimental study of similar conditions in animals.

3. Therapeutic experiments on nephrectomized animals under above conditions.

4. Therapeutic experiments with kidney extracts on nephritics with or without uremia.

5. Metabolism studies in chronic nephritis in man.

6. Metabolism studies in animals with partial extirpation of kidney.

7. Experimental study of the effect of kidney extracts on the blood pressure.

8. Studies of the effect on the heart and blood pressure of the removal of large portions of the kidney.

9. Studies of the effect on the blood pressure of the serum of animals with experimental nephritis.

10. Studies of the relation of chronic interstitial nephritis to increased secretion of the adrenal and the influence of the latter upon the cardiovascular system.

11. The determination, by physiologic methods, of the presence of adrenalin or adrenalin-like substance in the serum of nephritics or of animals with lesions of the kidney.

12. The study of nephrotoxic and endotheliotoxic substances in the serum of animals with experimental nephritis.

The first five of these may be disposed of briefly.

I. CLINICAL OBSERVATIONS.

These offer the most suggestive evidence of some influence which prevents the appearance in individuals with obstruction or accidental ligation of both ureters of the uremia which so early appears after complete nephrectomy. For example, in 66 per cent. of Fowler's series of ninety-three cases of ureter obstruction no marked uremic symptoms were evident. In such cases death is usually delayed for two weeks or more with few or no symptoms of uremia, while after nephrectomy it occurs usually in four to six days and commonly with well-marked uremic manifestations. That this difference may be due to an internal secretion is possible, but chemical or mechanical factors must be considered. It is known that the kidney has the power to form, from substances brought to it in the blood, certain new compounds, as, for example, hippuric acid from aromatic derivatives and glycocoll. It is possible that it has other synthetic or analytic functions, or perhaps a detoxicating power similar to that of the liver. Under such circumstances, even though the ureter were ligated, these functions would persist and control to a certain extent an autointoxication. It has been shown also, as the result of experimental studies, that urine is excreted until such time as the pressure in the dilated pelvis equals that of the blood. Under these circumstances the dilatation of the pelvis may become very great and a considerable quantity of fluid is contained therein; and it is possible that an exchange of fluids between pelvis and surrounding tissue may take place and thus, by allowing elimination of toxic substances through other channels, as skin, intestine or lungs, delay the symptoms which appear so rapidly after nephrectomy, a procedure which necessarily means an immediate and complete retention in the blood of the products of katabolism. Until the influence of such factors, and also of the nervous system, is settled experimentally we can merely look on clinical observations as suggestive of internal secretion but capable of interpretation in other ways.

II. EXPERIMENTAL NEPHRECTOMY AND URETER LIGATION IN ANIMALS.

In animals the recognition of symptoms which may be considered uremic is exceedingly difficult—practically impossible—and the only criterion available is the difference in time which elapses before death in ligation on the one hand and nephrectomy on the other. Such observations naturally receive the same interpretation as clinical experience.

III. THERAPEUTIC EXPERIMENTS ON ANIMALS.

Brown-Séquard and others, but more especially his pupils, have attempted to show that the life of the nephrectomized animal may be prolonged and uremia prevented by injecting extracts of kidney substance or the serum of defibrinated blood of normal animals, the blood being taken from the renal vein or sometimes, indeed, from the general circulation. These studies are not conclusive. The difference between the behavior of control and treated animals is but slight and the period of survival varies greatly in the control. For example, in the experiments of Ajello and Parascandalo twelve control dogs died in from four to forty-eight hours with dyspnea, convulsions and gastrointestinal disturbances considered to be uremic in character; while of ten treated with glycerin extracts, one lived four days, six three days, and the other three died in from forty-eight to fifty-two hours. Many other investigations, mainly of French and Italian workers, give similar results. The work of Meyer, a pupil of Brown-Séquard, is usually quoted in this connection. Meyer considered the dyspnea of nephrectomized animals, which he described as of a Cheyne-Stokes variety, to be the best criterion of the condition of uremia. Recording the respiration graphically, he took the momentary cessation of dyspnea resulting from the intraperitoneal injection of kidney extract, or intra-arterial injection of defibrinated blood of the renal vein, as a sign of improvement. His conclusions have been severely criticised on account of the ease with which, in such experiments, disturbances of respiration occur, the misleading nature of the method of recording and the influence of removing large quantities (60 c.c.) of blood from the circulation before injecting equal amounts.

The work on this subject shows that animals receiving extracts of the kidney or defibrinated blood of the renal vein certainly do appear to have a longer postoperative life; but the difference is slight and is not evident when the blood serum of the renal vein, which would be supposed to contain the internal secretion, is used, as in the experiments of Chatin and Guinard. From these latter experiments one is led to conclude that if serum of the renal vein is without effect, then either the internal

secretion is carried by the red corpuscles, or the corpuscles in some way aid in prolonging the postoperative life of the nephrectomized animal. From a survey of the literature one gathers the impression that these therapeutic experiments are of no value as support of the theory of internal secretion.

IV. THERAPEUTIC EXPERIMENTS ON MAN.

These were first attempted by Dieulafoy, who recommended the subcutaneous injection of glycerin extracts of the kidney of the guinea-pig and the ox under the name of "nephrine." This method was exploited by many in the treatment of nephritis and especially of uremic crises. Other preparations of the kidney, fluid and dry, and even injections of the blood of the renal vein were employed, but the favorable results at first reported were not constant and soon were regarded as coincident with the periods of temporary improvement so frequent in nephritis. Renal opotherapy has apparently been almost entirely abandoned. In Kaufmann's summary (1905) of the literature of the subject there are few references to its use in recent years. With its disappearance as a therapeutic measure disappears also one of the arguments in favor of the internal secretion of the kidney.

Somewhat different from opotherapy are the recent experiments of Carnot and Lélièvre, who have injected subcutaneously or given by mouth the serum and kidney extracts of animals which had withstood a unilateral nephrectomy. They assert that such treatment stimulates the regeneration and growth of kidney parenchyma, even to the extent of the formation of new glomeruli and tubules. This influence they term "nephropoietic."

V. METABOLISM STUDIES ON MAN.

The occurrence of uremia without nitrogen retention, and, on the other hand, the absence of uremia with decided nitrogen retention, has led to the suggestion that uremia might be due to a gradual diminution of the internal secretion of the kidney rather than to a retention of the products of metabolism. Owing to our lack of knowledge of the real nature of uremia this view, which certainly is suggestive, has some support.

It is well known, as pointed out by von Noorden, that in non-uremic nephrities the protein katabolism follows the same course as in health. If such individuals be given a diet which in a normal individual would establish nitrogenous equilibrium, any of the following results may occur:

a. The excretion of nitrogen through the kidneys and in the feces may correspond to the quantity introduced. This normal condition may occur especially in renal cirrhosis.

b. The quantity of nitrogen excreted may be markedly less than that ingested. This may be explained in part by increased elimination by the lungs, intestine or skin, but is also in part a nitrogen retention.

c. More nitrogen may be present in the urine than has been ingested. This is due to an increased permeability of the kidney and is analogous to the increased elimination of nitrogen resulting from the administration of large quantities of water.

These conditions may occur in any of the types of renal disease and may alternate in a single individual. As emphasized by von Noorden, the second type, or that of retention in renal cirrhosis, is seldom permanent, for it is succeeded either gradually or suddenly by one in which nitrogen is freely excreted and which restores the general daily average of nitrogen elimination.

On the other hand, almost all observations regarding the metabolism of patients suffering from uremia show a more or less considerable retention of nitrogen. The cases of uremia with excellent elimination of nitrogen are exceptions and, as von Noorden points out, recall "an old remark of Bortels that uremic convulsions sometimes occur when edema is already diminishing—at a time, that is, when nitrogenous extractives return from the tissues into the blood in large amounts, and so come in contact with the nervous system."

It would appear, therefore, that the detailed study of the metabolism of nephritis does offer a possible explanation of uremia in the absence of nitrogen retention without the aid of the theory of internal secretion.

VI. METABOLISM IN EXTIRPATION EXPERIMENTS ON ANIMALS.

From the experimental side we have the observations of Bradford and of Bainbridge and Beddard. The former, working with dogs, found that after the removal of approximately three-fourths of the total kidney weight death occurred in from one to six weeks from asthenia with great wasting; coma and convulsions were not observed.

Death is apparently dependent on the amount of kidney substance removed and not on the mutilation inflicted by the operative procedure. Excision of a portion of one kidney or portions of both is followed by an increase in the volume of the urine but unaccompanied by an increase in the total solids. The latter does occur, however, after excision of three-fourths of the total kidney weight. This increase is absolute when appetite does not fail, and relative when little or no food is taken. Under the latter circumstances the amount of urea eliminated is as great as that

excreted previously on a full diet. At the same time the blood and tissues, particularly the muscles, show a considerable increase in nitrogenous extractives. Bradford concludes that the disturbance of metabolism following the reduction of kidney substance is due, not to the retention of the products of normal destruction of tissue, but to an increased tissue katabolism, especially of the muscles, producing large quantities of urea. He states that he has made no observations to determine whether or not this is due to the cessation of the action of a renal internal secretion. His results have, however, been so interpreted by later writers.

Bainbridge and Beddard in a recent publication describe their observations on cats. They conclude that the removal of three-fourths of the kidney substance causes loss of appetite, wasting and death in a few days or weeks; that an increase of nitrogen in the urine is not constant and occurs only during the last few days of life when the animal has lost 22 per cent. or more of its body weight and, therefore, that the kidney has no direct influence on metabolism but that the increase of nitrogen is the result of inanition and similar to that which occurs in starving animals. They also find that there is not necessarily an increase in the volume of urine.

The difference of opinion between these investigators seemed sufficient to warrant a repetition of the experiments in order to determine the effect of the reduction of the kidney on nitrogenous metabolism. In carrying out the same I have also investigated the feces in order to determine, if possible, whether or not the inanition could be explained by digestive disturbances due to faulty absorption or possibly to the effect of irritating substances eliminated through the intestines as the result of faulty chemical correlation.

These experiments were made on dogs which were kept for some time before operation and during the entire course of the experiment in nitrogenous equilibrium. For this purpose a purin-free diet of casein, cracker dust and lard was used and the daily amount of water limited to 600 c.c. The animals were kept in the usual well-ventilated metabolism cages and were catheterized at the end of each twenty-four hours. After each catheterization the bladder was washed out and the wash-water added to the catheterized urine and that voided naturally and the whole made up to a definite volume. This urine was carefully preserved from changes of any kind until the analyses were made. When albuminuria occurred, which occasionally happened during a short period immediately following operation, the coagulable protein was removed by heat and acetic

acid, the coagula being thoroughly boiled out with water and the washings added to the urine.

On these twenty-four-hour samples the following determinations were made: Total nitrogen by the Kjeldahl method; ammonia by the Shaffer method, and urea by the Mörner-Sjoquist method. The investigation was so delimited mainly because the changes in total nitrogen and in the elimination of urea and ammonia were the only points in dispute and in part on account of the negative nature of the results obtained by Bradford and by Bainbridge and Beddard in regard to other substances.

The general procedure was to place the animal in nitrogenous equilibrium, conduct control determinations for a period of three days, operate, and after allowing two or three days for recovery from the acute effects of the operation, make determinations during one or more three-day periods. The operative procedure differed somewhat from that of the English investigators. Instead of a wedge of kidney substance, the upper half of the kidney was removed and the bleeding from the cut surface controlled by mattress suture. This method, although it narrows the pelvis somewhat, is not followed by extensive infarction or hemorrhage, and gives better results than that recommended by Bradford. At a subsequent operation either one-half the opposite kidney or the entire kidney was extirpated, and in the case of the former the remaining half was taken out at a third operation. In some instances one entire kidney and half the opposite kidney were removed at one operation without any immediate ill effect. The present work includes metabolism studies on but four dogs with varying degrees of kidney reduction; but a somewhat exhaustive study of the general effects of extirpation and of the process of repair in the kidney after various forms of operative injury will be presented later by Dr. J. A. Sampson and myself.[1]

At present it is sufficient to state that we have had no difficulty in keeping animals alive and in good condition with neither general nor local disturbances after the removal of one-quarter, one-half or, in some instances, three-quarters of the total kidney substance at one operation. The removal of larger amounts, and occasionally of three-quarters, is followed by severe general disturbances which have rendered futile all attempts to maintain the animal in nitrogenous equilibrium. In one instance after removal of a considerable portion of the kidney substance, a nephritis developed, which added to the value of the experiment rather than otherwise.[2]

The results in the four experiments thus far completed may be summarized as follows:

1. For details of these experiments see Jour. Exper. Med., 1908, x, No. 6.
2. For details and tables see Jour. Exper. Med., 1908, x, No. 5.

The first experiment shows no appreciable changes in metabolism after the removal of one-half of one kidney or one-half of each kidney. This animal unfortunately died a few hours after the third operation with no lesions discoverable at autopsy except a very extensive edema of the lungs.

The second experiment indicates that the removal of three-fourths of the entire kidney substance at one operation does not interfere with the general condition of the animal, as shown by the constant weight and normal metabolism figures.

The third experiment, on an animal with a spontaneous nephritis, a condition occasionally found in stray dogs, shows that this lesion has no effect on metabolism, even after the kidney substance is reduced one-half by a unilateral nephrectomy.

The fourth experiment was not planned for a study of metabolism, but when it was found that an animal with but one-quarter of its kidney substance had developed an acute nephritis, thus diminishing, it was assumed, the functional capacity of the fractional portion of the kidney remaining, it seemed too good an opportunity to lose and the animal was placed on a constant diet and the metabolism experiments carried out six days later. This animal, despite the great reduction of kidney substance and the presence of a nephritis, had a normal metabolism during the first three days' observation period. Two weeks later, however, when its appetite had begun to fail, equilibrium was lost, although no change in the percentage relations of nitrogen was evident.

After another period of two weeks had elapsed, however, and the kidney substance had still further been reduced by operation, leaving the animal with but one-seventh of its original kidney weight, a change in the urea-ammonia ratio, indicative of inanition, occurred. That this final change was due, as Bainbridge and Beddard state, to inanition there can be no doubt. Up to this point, the beginning of starvation, the changes in urea described by Bradford were not observed, and there is no evidence that the kidney, through an internal secretion or otherwise, has any influence on general nitrogenous metabolism. I believe that the theory of internal secretion, as far as it concerns general metabolism at least, may be set aside.

There remains, however, the very important question of why the removal of more than three-fourths of the kidney substance leads to loss of appetite and consequent inanition. Although occasional vomiting occurred in these animals it did not seem to be sufficiently frequent or severe to indicate a general gastrointestinal disturbance. To test this point extirpation of the kidney was done on two dogs after the establish-

ment of a gastric fistula. In this way it was hoped that the food necessary for nitrogenous equilibrium could be introduced artificially, and by examination of both urine and feces some light might be thrown on the cause of the disturbance. These efforts were rendered futile, however, by the inability of the stomach to retain the materials introduced. The conclusion is inevitable, therefore, that although the kidney appears to have no direct influence on nitrogenous metabolism, the removal of large portions of its substance does indirectly lead to disturbances of general nutrition, apparently by interfering with the functions of the alimentary canal.

The occurrence of these serious gastric and intestinal disurbances in animals after kidney reduction and their general similarity to lesions occurring occasionally in man in the course of chronic nephritis led me, in view of the more recent ideas of the chemical control of the body and the influence of one secretion on another, so well brought out by Starling and Bayliss' investigations, to study the feces of these animals in order to determine if partial nephrectomy had any influence on digestion, absorption or elimination into the intestine. Bainbridge and Beddard's claim that the disturbances in metabolism are due to inanition dependent on vomiting and diarrhea with eventual failure to take food, and not to direct influence of the kidney on metabolism, dodges the question. The point to be determined is whether or not these gastric and intestinal disturbances are caused by faulty absorption or by digestive disturbances due to the elimination into the intestine of substances normally removed by the kidneys. The demonstration of such a relation would be important not only as an illustration of the chemical inter-relationship between various organs, but would also aid in explaining similar disturbances associated with the nephritis of man.

These latter, which, I understand, are frequently so severe as to present symptoms closely resembling a violent gastroenteritis, have been ascribed in part to alterations of the mucosa due to edema, and in part to the influence of the uremic condition on the central nervous system. While these explanations account for many of the symptoms, others, according to von Noorden, must be attributed to toxic chemical action. In fact, recent investigations show that in uremia substances usually eliminated by the kidneys are secreted vicariously into the alimentary tract. Of these the most irritating chemically is ammonia, which is formed in the intestine by decomposition of the secreted urea. The feces of uremic diarrhea have been found to be extremely rich in ammonia.

Studies of the feces having for their object the determination of the degree of absorption in nephritis, for which we are indebted mainly to

von Noorden, show that the absorption of fats is very complete. The situation in regard to nitrogen is not so clear, the loss in some cases being greater than normal, while in others an abnormally high percentage is found. The variation in some individuals, without a corresponding change in diet, or in the nature of the stools, or in the general condition and with no change in the percentage of dry substance or fat content of the feces, led von Noorden to the conclusion that the increase of nitrogen was due, not to impaired absorption, but to the vicarious excretion of metabolites stored up in the organism. In many cases the excretion of nitrogen remains normal. High amounts, above three grams daily, are found in nephritis only in uremic diarrhea and are due largely to a high content of ammonium salts, constituting sometimes 10 to 20 per cent. of the total fecal nitrogen.

In the four experiments summarized above the total nitrogen in the feces evacuated during control periods and periods of metabolism study was estimated. The results indicate no marked change in the total nitrogen or its percentage relation. The inanition and gastrointestinal disturbance can not, therefore, be explained by impaired absorption or by an undue elimination of protein substances. The increased elimination of toxic substances, non-nitrogenous in nature, may be a factor, but on this point I have no observations.

I now pass to another phase of my subject, the influence of the kidney on the cardiovascular system. Here experimental methods have added little to the knowledge based on clinical and anatomic study.

VII. THE EFFECT OF KIDNEY EXTRACTS ON BLOOD PRESSURE.

Tigerstedt and Bergman in 1898 detailed a very extensive series of experiments which appeared to demonstrate the presence of a pressor substance in extracts of the kidney of the rabbit. This substance was obtained from the cortex of the kidney and was present not at all or only to a slight extent in the medulla. It could be extracted from the fresh organ by salt solution, by alcohol, by fresh blood and to a less extent by cold water. Extracts prepared by boiling gave no effect. The substance was non-dialysable and the investigators, therefore, concluded that it could not be any of the salts of the urine. To this substance they gave the name "renin" and regarded it as an internal secretion of the kidney normally passing into the blood. The rise of pressure, which varied from a few millimeters to 25 or 35 mm. Hg., they believed to be due to an action on the peripheral nerve centers as well as possibly on the spinal cord. Very small amounts caused as much effect as larger doses, and repeated injections produced each an effect as great as the first injection.

In order to demonstrate the passage of this supposed pressor substance into the blood they injected blood from the renal vein into the vessels of rabbits which had suffered double nephrectomy. A moderate rise followed; for example, in one animal, twenty-four hours after nephrectomy, a rise of 18 mm. Hg. occurred. These last experiments were repeated by Lewandowsky the following year, and although Tigerstedt's rise of pressure was confirmed, Lewandowsky obtained a similar transient pressor effect in his controls by injecting blood from the general venous (jugular vein) and also arterial systems. The rise he considered to be due in part to the rapidity of injection, but as it was not obtained by injections of salt solution, he concludes that the effect is due to some substance or substances in defibrinated blood capable of pressor effect but not to an internal secretion of the kidney.

Lewandowsky's results appear to have discouraged the further extensive investigation of Tigerstedt's observations, which one would have expected. The only references in the literature, at least as far as I have been able to determine, are those of Livon, Fiori, Vincent and Sheen, and Shaw. Of these the first two describe a pressor effect; Vincent and Sheen various results, sometimes a fall, sometimes a rise in pressure, and occasionally no effect. Shaw, using the cat, almost uniformly obtained striking and prolonged rise in pressure varying from 1 to 72 mm. Hg. Mention must also be made of the observation of Oliver, published a year before those of Tigerstedt. Utilizing the frog's exposed mesentery to determine the effect of various organ extracts on the peripheral vessels, he obtained constantly, with adrenal extract, a most decisive contraction but no invariable effect with extracts of the kidney and various other organs.

When one analyzes these investigations the striking fact is brought out that the result seems to depend on whether or not the kidney extract was injected into an animal of the same species. Thus Tigerstedt, in a series of about fifty experiments with the rabbit, obtained uniformly a pressor effect, as did also Shaw—using the cat—in all but one of nineteen injections. Vincent and Sheen's injections were not always into animals of the same species, and their results varied. Livon does not give the details of his injections, but his results were uniform, as also appear to have been those of Fiori, whose original paper I have, however, not seen.

The uniformity of these results with kidney extracts, when considered in the light of the fact that other organs, as liver and spleen, appear to contain a depressor substance, led me to repeat these experiments, with various modifications, in the hope of determining whether or not

the pressor effect of the kidney extract was due to a peculiar function of the kidney or to some other factor, physical or chemical in character. The desirability of more light on this question must be evident to any one familiar with the several theories, based on the principle of internal secretion, which have been formulated by clinicians to explain the hypertension and heart hypertrophy associated with chronic nephritis. It is sufficient to mention Riva-Rocci, who states that a blood-pressure-raising substance is formed in increased amounts in the diseased kidney; and Shaw, who attempts to offer a basis for Traube's theory of uremia by assuming that the substance causing arteriospasm and thus producing cerebral disturbances without postmortem lesions is possibly the pressor substance "renin."

The results of my experiments offer no support to the theory that a pressor substance or substances exist in the normal kidney. Early in the investigation a curious contradiction was observed. It was found that the injection into the rabbit of extracts of either dog or rabbit kidney caused a slight rise in pressure, but that similar injection into the dog caused a depressor effect, which, when dog's kidney was used, was very decided. From these observations it was evident that the pressor substance of the kidney of any given species has no constant pressor effect for animals of other species, as is the case with adrenalin. In attempting to analyze these results it was found that almost any substance injected into the rabbit's circulation in dose of one to three cubic centimeters caused a slight transient rise in pressure. These substances included blood serum, defibrinated blood, urine, extracts of the liver of both rabbit and dog, solutions of urea, of sodium chlorid and Locke's solution. The production of a rise of pressure by such a variety of substances detracts greatly from the significance of the rise following the injection of kidney extracts and indicates that in an animal, as the rabbit, whose circulation is easily disturbed, the effect of the injection is largely if not entirely mechanical. Other experiments demonstrated that the rise in pressure could be obtained with filtrates of the heated extract and with its dialysate, contrary to the statement of Tigerstedt and Bergman.

The dog's kidney extract was studied in the hope of removing the depressor substance and demonstrating a pressor substance. All such attempts have been unsuccessful. It has, however, been possible to show that the depressor effect is due apparently to the salts of the urine and not to any peculiar constituent of the kidney cells. This was brought out by observations which showed that extracts of other organs of the dog had little or no depressing effect, while the urine had a depressor effect equal to or greater than that of the kidney extract. Also the substance

was not destroyed by heat, or autolysis, was not precipitable by alcohol and dialyzed readily. Experiments to demonstrate the presence of cholin were negative.

VIII. EFFECT ON HEART AND BLOOD PRESSURE OF EXTIRPATION OF LARGE PORTIONS OF THE KIDNEY.

The recently published investigations of Pässler and Heineke have aroused a new interest in the experimental study of the relation of the kidney to increased blood pressure and cardiac hypertrophy. These investigators found that after the removal of a considerable portion of the kidney substance, approximately two-thirds to three-fourths by successive operations, a rise of blood pressure occurred which was permanent and associated with cardiac hypertrophy. This result was not constant, but occurred in about 25 per cent. of the animals which survived by at least four weeks a considerable reduction of kidney substance. In such it was observed also that arterial spasm with further rise of blood pressure quickly followed stimuli which in normal animals would produce little effect. These observations suggest that the heart hypertrophy is due to increased work resulting from the circulatory disturbances caused by tendency to arterial spasm, and that the vascular spasm is due in its turn to the effect of retained toxic substances. A similar hypertrophy of the heart in dogs after kidney extirpation had previously been observed by Paoli. Bradford states that in dogs with three-quarters of the kidney removed "the blood pressure remains high" even in animals extremely cachectic, but no obvious cardiac hypertrophy is found. There is every reason to believe that the observations of Pässler and Heineke will be confirmed; if so, we shall have valuable evidence of a chemical correlation of extreme importance in explaining the cardiovascular lesions of nephritis. This confirmation has been a part of my present study, but thus far I have accomplished little, as most of the animals with considerable kidney reduction have been used for other purposes.

IX. THE EFFECT ON BLOOD PRESSURE OF THE SERUM OF ANIMALS WITH EXPERIMENTAL NEPHRITIS.

Assuming that if reduction of kidney substance leads to retention of toxic products affecting blood pressure, the acute forms of experimental nephritis would have a similar effect, I have conducted a series of blood-pressure experiments along that line. The serum of dogs poisoned with uranium nitrate and potassium chromate has been obtained at various stages of the course of the experimental nephritis and injected in doses of twelve to twenty cubic centimeters into a branch of the femoral vein of normal dogs. The pressure was taken in the carotid. The results

have been somewhat surprising. While the serum of a chromate nephritis almost uniformly causes a slight rise in pressure, the injection of the serum of uranium dogs is followed by a decided drop.

That the drop caused by uranium serum is not due to traces of the uranium nitrate injected is shown by the fact that small amounts (0.0075 gr.) have no effect on the blood pressure, while larger amounts (0.0375 gr.) have a pressor effect.

Similar experiments with rabbits give, with both uranium and chromate sera, a definite continuous rise very different from the slight transient rise caused by kidney extracts. In these animals a drop was never observed.

It is evident, therefore, that disturbance of kidney function does cause the appearance of substances in the blood serum which have a definite effect on the blood pressure. The variation in this effect is suggestive. Potassium chromate produces parenchymatous changes in the kidney, while uranium appears to affect both tubular and vascular structures. The difference in action of the two sera may possibly be explained by this difference in disturbance of function. More work along this line is essential.

It matters little whether the substances causing these pressure effects are retained products of metabolism or are products increased by the vicarious action of other organs or, for that matter, are the result of an internal secretion of the kidney itself. It also is a matter of indifference whether the immediate effect is pressor or depressor. The important point is that in disease of the kidney there occurs in the blood serum in increased amount a substance or substances affecting blood pressure and, therefore, of supreme importance as evidence of chemical correlation in the pathology of diseases of the kidney.

X. RELATION OF THE ADRENAL TO CHRONIC INTERSTITIAL NEPHRITIS AND ARTERIOSCLEROSIS.

Of considerable interest at the present moment, in view of the investigations of French clinicians, is the question of the relation which the adrenal bears to the arterial hypertension and degeneration of Bright's disease. It would appear but natural, in view of our knowledge of the influence of adrenalin in raising blood pressure, of the experimental lesions produced in the rabbit by this substance, and of the clinical phenomena of chronic nephritis, to associate the renal and arterial disturbances with some disturbance of the adrenal. At first glance it is difficult to determine whether the condition in the kidney is responsible for changes in the adrenal leading to an increased outpouring of the secretion and consequent arterial hypertension and degeneration, or whether

the renal changes are secondary to arterial disease caused by a primary adrenal disturbance. Within the past three years French investigators, led by Vaquez, have offered a large mass of literature which indicates that nodular or diffuse hyperplasia of the adrenal is commonly associated with contracted kidney and arteriosclerosis when the disease does not run too rapid a course. The hyperplasia is considered as an indication of a hyperactivity of the antitoxic and angiotonic functions of the gland, what we might call, perhaps, hyperadrenalism.

To indicate the observations on which this theory is based, a portion of the literature may be reviewed briefly:

The first case described by Vaquez was one of adenoma of the cortex of the adrenal associated with a contracted kidney. Josué described three instances of diffuse arteriosclerosis with hypertrophy of the adrenal. Aubertin and Ambard, in eight cases of contracted kidney, found in three fatty adenoma, and in four diffuse hyperplasia; the eight, with a very rapid course, had a normal adrenal. Lemaire in a single instance, and Froin and Rivet in six out of seven nephritics found adenomata or nodular hyperplasia; the seventh, a patient with but slight rise in blood pressure, was negative. Menetrier found two adenomata in seven cases of contracted kidney. These figures indicate the frequency of changes in the adrenals in association with renal and vascular lesions. There are many negative findings, however, and the frequency of similar lesions with diseases other than those of the kidney and the vascular system has not been sufficiently investigated. Landau, who has examined the adrenals in sixteen cases of arteriosclerosis, finds no changes which might not be ascribed to the effect on the gland of arteriosclerosis itself.

In the hope of throwing more light on the subject by purely anatomic studies, I have examined the autopsy records of the Bender Laboratory and have attempted to determine the relation, on the one hand, of vascular lesions to changes in the adrenal, and, on the other, the association of the latter with chronic interstitial nephritis.[3]

The histologic examination of a large number of adrenals points conclusively to very definite and fairly constant changes in this organ in general arteriosclerosis. These changes, however, are not limited to the arteriosclerosis associated with contracted kidney, but are found also in arteriosclerosis accompanying the parenchymatous type of nephritis, and, finally, in general arteriosclerosis without evident chronic lesions of the kidney. The changes are of two types: first, those undoubtedly secondary to the alterations in the vessels of the adrenal, as thickening of the capsule, diffuse increase of connective tissue and round-cell infil-

3. For details of this study see Jour. Exper. Med., 1908, x, No. 6.

tration: and, second, various grades of hyperplasia, nodular and otherwise, variations in the amount of chromaffin substance and changes in the cytoplasm of the cortical cells. Whether these latter changes are also secondary to the arteriosclerosis or are independent, and perhaps primarily of importance in the production of a hyperadrenalism concerned in the etiology of the vascular lesions, I have been unable to determine, though I incline to the former view.

That these various changes occur more or less constantly in association with arteriosclerosis is a point of great interest and importance in the pathology of this disease and worthy of further study. In connection with the present study, however, the chief value of these observations lies in the fact that these alterations are not peculiar to chronic interstitial nephritis, with which disease the French particularly associate them, but are found also in other forms of chronic nephritis and, indeed, in all conditions with advanced arteriosclerosis. It would appear, therefore, on purely anatomic grounds, that a correlation between the diseased kidney and the adrenal having an influence on the vascular system is doubtful. It must be admitted, however, that this question can be definitely settled only by careful anatomic studies controlled by blood-pressure determinations during life.

XI. ADRENALIN OR ADRENALIN-LIKE SUBSTANCES IN THE SERUM OF NEPHRITICS.

Another phase of this subject is the attempt within the past year to demonstrate adrenalin or adrenalin-like substances in the serum of nephritics. For this purpose the observation of the Meltzers, that adrenalin causes a dilatation of the frog's pupil, has been utilized. According to Ehrmann, this reaction is sufficiently precise to allow of the determination of adrenalin in dilutions of 1 to 1,000,000 (0.1 mg. being the minimal blood-pressure-raising dose for the cat).

Schur and Wiesel have found that the serum of patients with chronic nephritis, even when diluted twenty times, uniformly causes mydriasis of the frog's enucleated eye. This result does not occur with the serum of normal individuals or of individuals with other diseases. A similar dilatation is caused by the serum of nephrectomized rabbits, but not by that of the normal rabbit. Eichler confirms the results of Schur and Wiesel in regard to the serum of nephritics and that of nephrectomized rabbits, and considers the question of whether or not the relation is one of the internal secretion of the kidney to that of the adrenal. Kaufmann in discussing the results of Schur and Wiesel, states that he obtained a very definite dilatation in two cases of chronic nephritis, but also a slight

dilatation with the serum of normal individuals and of individuals suffering from other diseases.

Schlayer has attempted to demonstrate pressor substances by utilizing the "vessel strip" method. This method, originated by Meyer, consists in fastening a strip of the carotid of the ox, obtained by cutting out a ring of the vessel, to the bottom of a small glass jar, and to the other end a ligature leading to a two-armed lever, one arm of which writes on a smoked drum. Fluids to be tested are placed in the jar containing the "vessel strip." Meyer studied the effect of a variety of substances on such vessel preparations and found the vessel to respond by contraction to very minute amounts of adrenalin (0.000,015 mg. in 15 c.c. of Ringer's solution). He also found that normal blood serum caused a very definite contraction of the vessel.

Schlayer used this method for testing the serum of nephritics. His control experiments demonstrated the power of normal serum to cause contraction, and his observations on the effect of concentration, dilution, dialysis and heating showed practically the same effect on the action of the serum as these measures have on the action of adrenalin. He concludes, therefore, that in normal serum is present a substance having some of the physiologic as well as the physicochemical characteristics of adrenalin. Assuming, therefore, that whether or not this substance is adrenalin, it would be increased in the serum of nephritics, if responsible for the increased blood tension, he conducted a series of experiments with sera of patients with various forms of chronic nephritis. Twenty-six observations on sera of eight different patients, with blood pressure of 190 to 260 mm. Hg by von Recklinghausen's apparatus, were made. Only two sera, one from an individual with a small primary contracted kidney and one from a patient with chronic lead poisoning (contracted kidney) gave a reaction greater than that of the control serum. In all others, all contracted kidneys, the effect was less. After ruling out weakening of the active substance by dilution, due to the hydremic condition of the nephritic serum, he concludes that the results do not support the adrenalin theory of high pressure in chronic nephritis. Furthermore, he minimizes the importance of Schur and Wiesel's experiment, for, as he argues, as the pupil test is negative with normal serum while the "vessel strip" reaction is positive, the substance in nephritic serum causing mydriasis can not be the same as the blood-pressure-raising substance. In reply to this criticism Schur and Wiesel suggest that Meyer's method indicates the presence of a pressor substance other than adrenalin and that, therefore, the subject should be more thoroughly investigated. In support of their own position they emphasize the point that from the

serum of nephritics can be isolated a substance giving the iron chlorid reaction for adrenalin.

I have attempted to control these results, but have been unsuccessful, in part because I could not obtain satisfactory tracings with Meyer's "vessel strip" method, and in part on account of the difficulty of obtaining the sera of nephritics. The frog's pupil test I have applied to the serum of four dogs with severe chromate nephritis, three with uranium nephritis, and one with spontaneous chronic nephritis, with entirely negative results. The serum of uranium and chromate rabbits also give negative results.

These investigations with the sera of animals with acute experimental nephritis are, however, in no way analogous to those with chronic nephritis in man. The observations of Schur and Wiesel, on the one hand, and of Schlayer, on the other, are of great importance and should be repeated by those having access to abundant clinical material.

XII. NEPHROTOXIC SUBSTANCES.

The theories concerning nephrotoxic immune serum, or, as it is generally termed, "nephrotoxin," harmonize with some of the statements put forth concerning the internal secretion of the kidney and with the theory of chemical correlation. But a few years ago all kinds of cells were injected in various ways into animals of alien species in the hope of producing specific cytotoxins for any and all of the tissues of the animal body. The theory underlying these procedures assumed that the injected cells contained substances capable of stimulating the cells of the injected animals to the formation of antibodies. It assumed virtually, therefore, that the cells introduced contained, for example, in the case of kidney cells if thoroughly washed free of blood and urine, substances peculiar to cells of that organ and not occurring in the cells of other organs. Such reasoning could well be turned to support the theory of internal secretion by assuming that the substance causing the immunization was the internal secretion of the kidney set free by the disintegration of the injected cells. The theory of the nephrotoxins, however, was even more comprehensive, and the results of such immunization experiments were applied to chronic nephritis. The hypothesis was put forth that in this disease the continued destruction of renal cells led to the formation of a lytic body, autonephrolysin, capable of the continued destruction of other renal cells, a sort of vicious circle, as it were, which explained many of the complications of the disease. On this supposition a number of investigators have attempted to demonstrate in animals that the ligation of the vessels of one kidney leads to the escape from the injured kidney of a substance (autonephrolysin) which has the power

to impair the function of the other kidney, or that the serum of such an animal introduced into the vein of a normal animal of the same species would cause albuminuria and histologic evidence of renal impairment (isonephrotoxin). Although the results of such experiments have been more or less contradictory, they indicate, I think, a theoretical analogy at least between the theory of nephrotoxins and that of internal secretion. The observation of Ascoli, for example, that a nephrotoxic serum caused an increased blood pressure, coupled with the statements of Riva-Rocci and Maragliano that a similar substance is found in increased quantities in the diseased kidney, has been freely quoted as an explanation of the increased arterial tension and cardiac hypertrophy of patients with renal disease. Unfortunately, however, for this relation carefully planned experiments do not support the theory of specificity of the cytotoxins. In my own work on this subject, done largely in this city while associated with the University of Pennsylvania, I demonstrated that a true specificity of nephrotoxins did not exist, that the production of autonephrolysin by injuring one kidney was doubtful, and that Ascoli's claim for a blood-pressure-raising substance could not be confirmed. These conclusions have been supported almost uniformly by later investigators.

There is, however, a phenomenon brought out by the investigation of nephrotoxic sera which remains unexplained and which I think is of peculiar interest in connection with any discussion of the influence of the normal or diseased kidney on the functions of the body. I refer to the observation of Lindemann that the serum of an animal suffering from an experimental potassium-chromate nephritis has the power to produce lesions of the kidney when introduced into a normal animal, and also to my own observation of similar results when the serum of dogs with spontaneous nephritis or of those with lesions due to nephrotoxic immune serum, as also noted by Bierry, are introduced into normal dogs. Such injections cause the excretion of albumin and casts and histologic changes in the kidney. These observations, which, so far as I am aware, have never been questioned, indicate the presence in the serum of a substance formed anew during a nephritis, or accumulating as the result of retention and, therefore, of great importance from the point of view of chemical correlation. The phenomenon is quite distinct from that of the action of a substance produced by immunization, as it represents presumably the action of a substance resulting from tissue destruction or faulty function or both.

Ever since my first experiments on this subject in 1903 I have intended to take up this problem more in detail, but have had no opportunity until the obligation of making this address forced it on me.

Experiments along the general lines suggested I have carried out in association with Dr. H. P. Sawyer. Thus far in our investigations we have made nine observations concerning the nephrotoxic action of the serum of animals with nephritis.[4] Two out of three dogs receiving the serum of animals with uranium nephritis and four of five receiving the chromate of potassium serum have given positive results. The serum of a spontaneous nephritis gave a positive result in the one experiment in which it was tried. In all instances the animals were isolated for some time previous to injection and their urine carefully examined for albumin and casts. As I have shown elsewhere, this precaution is very important in view of the frequency with which spontaneous nephritis occurs in the dog. The serum was injected either into a vein or into the peritoneal cavity in doses of ten to forty cubic centimeters. The elimination of albumin was definite but usually in small amounts. In but two experiments could it be estimated by the Esbach method, amounting in one experiment to 0.25 per cent., and in the other to 1.5 per cent. Casts appeared sometimes on the first day, but more frequently on the second, and were accompanied by numbers of renal epithelial cells and usually by a few white blood corpuscles. This condition of the urine lasted for but a few days, as a rule, though sometimes the return to normal was delayed for a week or more. Control experiments with normal sera were negative.

Similar experiments with rabbits have been tried, but with absolutely negative results. The sera of rabbits with chromate, uranium and spontaneous nephritis, and of the nephritis produced by injecting nephrotoxic immune serum, have been injected into the ear vein in dose of five to twelve cubic centimeters without the occurrence of albuminuria.

The possibility of carrying over in the serum, in the experiments on dogs, minute amounts of the salts injected must be considered, but it has been impossible to detect these salts in the filtrate of the serum concentrated after coagulation. The tests employed, however, are not so sensitive as entirely to exclude the persistence of these salts. On the other hand, if present they would occur in such minute amounts that it seems improbable that they could have anything to do with the lesion described. Certainly they appear to have had no effect in the experiments with rabbits.

The direct action of these various sera on renal cells has been determined also by adding the sera to freshly-prepared mixtures of kidney

4. For completed study see Jour. Med. Research, 1908.

cells after the manner carried out in the testing of cytotoxic immune sera. No agglutinative or cytolytic action was evident.

The very definite physiologic disturbance seen in these animals, in view of the experience of Lindemann and Bierry, give a definite basis, it appears to me, for assuming that the serum of dogs with nephritis contains nephrotoxic substances. In view, however, of the negative experiments with rabbits it is manifestly impossible to assume that the serum of man also contains these bodies during the course of nephritis.

STUDIES OF EDEMA.

Most recent investigations of edema have had to do with the questions of salt retention and water balance—problems to which purely physical methods may be applied. The recent studies of the edema of uranium nephritis, and especially of Heineke's observations on the apparent power of the serum of an animal poisoned with uranium to produce edema, opens up, on the other hand, the possibility of an explanation of some phases of the problem by chemical correlation.

Uranium nephritis, in rabbits at least, is accompanied, as first shown by Richter, by a well-marked edema of the subcutaneous tissues and hydrops of the pleural and peritoneal cavities—a condition which does not obtain in animals poisoned with chromic salts, cantharidin, aloin and other renal irritants. Of greater interest from the point of view of chemical correlation is the observation that the serum of an animal with uranium nephritis, when introduced into an animal with a chromate nephritis, causes the development of a well-marked edema. This phenomena, first observed by Heineke and since confirmed by Blanck, who, however, finds it to be not a constant occurrence, suggests that, in addition to the presence of nephrotoxic substances in the serum of animals with nephritis, there may also occur substances which have an injurious effect on the somatic endothelial cells. It, therefore, offers a new method of experimentation for determining the relation of hydremia to renal injury and endothelium destruction in the production of edema. Two explanations seem possible: either the retention, as the result of the kidney insufficiency, of substances which act as lymphagogues of the second order; or the injurious action on the endothelium of some substance or substances causing an alteration in its permeability to fluids.

In this connection it is impossible to go into the question of the mechanistic versus the vitalistic theories of lymph formation. It is sufficient to recall that of the latter theories Heidenhain's, as well as Hamburger's, assumes an increased activity of the endothelial cells caused by katabolic products, and that Lazarus-Barlow and Asher believe

also in the influence of cell action, but of the cells of the organ rather than of the endothelia. Lazarus-Barlow further emphasizes the influence of waste products. And even Starling, who supports the purely physical theory, assumes an altered permeability of the endothelial membrane.

In connection with these theories of the physiology of lymph secretion we have certain views concerning the pathologic secretion of lymph which point to vascular injury as an important factor. Cohnheim and Lichtheim, in their well-known experiments on the production of hydremic plethora, found that the injection of large quantities of salt solution into the vein of rabbits and dogs, although it led to ascites and edema of the internal organs, did not cause edema of the normal skin and subcutaneous tissues; but if the skin was irritated, as by exposure to the sun, painting with iodin, or immersion in hot water, local edema of the skin always followed transfusion. From these experiments Cohnheim concludes that the mild irritation of the skin caused an alteration of the capillary walls which made them more permeable for the fluid of the hydremic plethora. Support of this theory is offered by the experiments of Magnus, who found that edema of the skin occurs in transfused animals if previously arsenic, which pharmacologists consider a specific poison for blood vessels, is injected, or if animals are in deep anesthesia from chloroform or ether. Magnus also found that in nephrectomized animals transfusion, if practiced within a day or two, leads to anasarca. Similar results have been obtained by Albu. Closely related to Cohnheim's theory of renal edema is that of Senator. The difference is that Cohnheim assumes that the altered permeability of the capillary wall is due to the action on these structures of toxic substances not eliminated as the result of the renal insufficiency. Senator assumes that the edema is as much primary as is the renal lesion, and that both are caused by the same toxic agent affecting the glomeruli of the kidney as well as the vessels of the skin, the toxic agent having its origin in the primary disease, as scarlet fever and malaria.

My own experiments have had for their object the production of edema by the administration of substances which would not only produce a renal lesion but also injure the vessels of the body generally; but more especially the object has been to demonstrate ultimately the presence of endotheliotoxic substances in the serum of animals with experimental nephritis—that is, to find support of Cohnheim's theory rather than Senator's, for the former is of greater interest from the point of view of chemical correlation.

Observations of this kind with sera are few in number. Heineke's experience with the serum of uranium animals has been cited. This

serum, from animals with edema, injected into animals poisoned with chromic salts, which, in his experience, do not cause edema, produced hydrops of the pleural and peritoneal cavities. His experiments were not reported in detail, but have been confirmed by Blanck, who, however, found that the condition could not be reproduced constantly.

In a later study with Meyerstein, Heineke reports the production of edema in 64 per cent. of the animals receiving uranium serum intravenously; but he also found edema in 60 per cent. of those receiving normal rabbit serum. In all instances the animals had been poisoned for four to five days with potassium bichromate and had received water and sodium chlorid by the stomach-tube. As this treatment in absence of serum injection did not cause edema, it is suggested that the serum in both instances had some injurious effect on the blood vessels.

In this connection should be mentioned also the observations of Kast and of Starling on the lymphagogic action of the serum of edematous nephritics when injected into animals. Kast injected into the vein of a dog seventy-five cubic centimeters of the serum of a very edematous individual suffering from chronic hemorrhagic nephritis and found the flow of lymph to be increased ten-fold. Sera from two other nephritics with edema increased the flow three-fold and two-fold respectively, while the serum of normal individuals and of nephritics without edema gave no results, as was also the case in one instance each of uremia and cardiac dropsy. Starling reports a single experiment on the dog in which it was observed that the serum of a uremic individual caused a marked quickening of the flow of lymph from the thoracic duct.

In my own experiments, in order to determine if any relation exists between vascular injury and kidney lesions, in the presence of hydremia, rabbits have been treated with substances known to be both renal and vascular poisons and hydremia has been produced by introducing by a stomach-tube considerable amounts (100 c.c.) of water. In other experiments a specific renal poison has been administered first and later a vascular poison or vice versa. The substances used have been the salts of chromium and uranium, arsenious acid, ricin, snake venom and nephrotoxic immune serum.

The most important experiments thus far completed have been those with arsenic and nephrotoxic immune sera. Arsenic, a renal and vascular poison, given in the absence of hydremia, produces a local edema about the point of injection which is not observed in simple chromate poisoning and indicates the toxic action of arsenic on the blood vessels. When accompanied by daily administration of 100 cubic centimeters of water by the stomach-tube there is observed a diffuse gelatinous edema

of the subcutaneous tissue of the abdomen with fluid in the thoracic and abdominal cavities. While this result indicates the necessary presence of hydremia in the production of edema, it also indicates the influence of a diffuse vascular poisoning. Diffuse edema after the use of a supposedly specific renal poison, as chromic salt, I have observed but once. It is, of course, the usual occurrence after the use of uranium, which is supposed to act as a vascular as well as a renal poison.

Peculiarly interesting results have been obtained by the intravenous and intraperitoneal injection of nephrotoxic immune serum into rabbits suffering from chromate nephritis. Control experiments had shown that while normal dog's serum, which is slightly toxic for the rabbit, did not cause edema in rabbits receiving a large amount of water by the mouth, it did produce in chromate rabbits, receiving the same excess of water, edema about the ureter and the pelvis of the kidney and in the mucosa of the bladder. As the localized edema was due apparently to the well-known toxic action of an alien serum affecting apparently the vessels along the path of elimination, the attempt was made to increase this toxic action by producing a nephrotoxic immune serum. This was done by injecting serum from the washed kidneys of rabbits into the dog. Such a serum, as is now well known, is not specific in its action; in addition to the nephrotoxic power it has also hemagglutinative and hemolytic properties and affects also, through these activities, the vessels of various organs. These latter properties were those most desired. The serum injected into chromate rabbits, receiving daily 100 cubic centimeters of water, caused uniformly edema of more or less extent. In one instance the subcutaneous edema involved not only abdomen and thorax but all four legs. The pericardial, pleural and abdominal cavities contained large amounts of fluid, and the retrosternal and mediastinal tissues and the fat about the pelvis of the kidneys were diffusely infiltrated.

To control this observation the same serum was injected into normal rabbits receiving an excess of water, with no results except a moderate but very definite edema of the retrosternal tissues, with in one instance a small amount of fluid in the pleural cavities.

A shorter series of experiments along the same general lines, except that water was not administered in excess, were made on dogs. The animals were well supplied with water, but none was administered by the stomach-tube. In none was it possible to produce edema.

These experiments are as yet incomplete and I am not prepared to draw definite conclusions. They confirm, of course, the general opinion concerning the relation of hydremia to the kidney lesion in the produc-

tion of edema, and to my mind point very strongly to the important part played by vascular poisons. The application of data derived from animal experiment to human pathology is not always safe, but these observations would appear to support the supposition that toxic substances accumulating in the blood may aid in the production of edema by an injurious action on vessel endothelium.

In conclusion, it is evident, I think, from this critical review and from the experiments which have been presented, that there is little to support the older theory of the internal secretion of the kidney, but, on the other hand, much to indicate that the application of the theory of chemical correlation to the pathology of chronic nephritis may aid in elucidating many doubtful phases of this disease. The evidence of such correlation, although not conclusive, is sufficient to warrant the utilization of all experimental methods, but especially those of physiology and biologic chemistry, in the hope of eventually adding to our knowledge of the obscurer principles concerned in the production of the important lesions associated with chronic diseases of the kidney. The presentation, in an orderly manner, of the possibilities of investigation in this territory and of some of the methods of attack have been the principal objects of this address.

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HISTOPLASMOSIS: A FATAL INFECTIOUS DISEASE RESEMBLING KALA-AZAR FOUND AMONG NATIVES OF TROPICAL AMERICA.*

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INTRODUCTION.

Histoplasmosis[1] is a term applied to a fatal infection by a protozoon, *Histoplasma capsulatum*, which has been encountered three times during the past two and one-half years in Ancon Hospital, Canal Zone, Panama. Clinically and pathologically the disease is suggestive of kala-azar,[2] a disease of India, characterized by irregular fever, emaciation and splenomegaly and by the presence of the Leishman-Donovan body in the tissues. The micro-organism responsible for the Isthmian infection is different from the Leishman-Donovan body, sufficiently so to warrant its being placed in a different order.

The condition was not discovered until the autopsies, and chiefly on that account cultural experiments were unsuccessful and clinical data meager.

HISTORICAL SKETCH.

Cunningham[3] published in 1885 an account of bodies found in the tissue obtained from a Delhi boil. Cunningham's technic was crude and the bodies measured 8.8 to 12.6 microns—altogether too large to be the bodies described later by Wright in a tropical ulcer called "Delhi sore."

In 1903 J. H. Wright[4] described micro-organisms found in smears and sections of tissue from an ulcer of the cheek. The patient was a native of Armenia, nine years of age. The ulcer had made its appearance some two or three months before the child left Armenia.

"The lesions consist essentially of a very extensive infiltration of the corium and papilla by cells accompanied by atrophy and disappear-

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*Read in the Section on Pathology and Physiology of the American Medical Association, at the Fifty-ninth Annual Session, held at Chicago, June, 1908.

1. Darling, S. T.: Maryland Med. Jour., April, 1907.
2. Rogers, Leonard: Fevers in the Tropics, Oxford Med. Publ., London, 1908.
3. Cunningham, D. D.: Scientific Memoirs by Medical Officers of the Army of India; Part I (1884), Calcutta, 1885.
4. Wright, J. H.: Jour. Med. Research, December, 1903, x; new series, v, 472-482.

ance of the epidermis of the part. The infiltrating cells are plasma cells, various kinds of lymphoid cells and large cells with single vesicular nuclei and a relatively large amount of cytoplasm in which are large numbers of micro-organisms.

"The micro-organisms in smears are generally round, sharply defined in outline, and two to four microns in diameter. A large part of their peripheral portion is stained a pale robbin's-egg blue, while their central portions are unstained or white. A very prominent feature is the presence in each of the bodies of a larger and smaller lilac-colored mass. The larger mass is about one-fourth or one-third the size of the body; is of variable shape, but always forms a part of the rounded periphery of the body.

"The blue peripheral portions of the bodies are usually sharply defined from the central unstained portion and sometimes show small unstained areas. A few of the bodies are oval or elongate in form." Wright proposed the name *Helcosoma tropicum* for the parasite.

Major Leishman,[5] R.A.M.C., described in May, 1903, certain small oval bodies obtained from autopsy spleen smears in a case of chronic dysentery, cachexia and low fever. Leishman had observed this body first in 1900. The patient had contracted the disease in Dum-Dum, near Calcutta, and died in London. Leishman described the bodies as being round or oval, and two to three microns in diameter. When stained by the Rowmonowsky method they were found to contain two masses of chromatin, a large circular mass or ring and another smaller mass usually in the form of a short rod set perpendicularly or at a tangent to the circumference of the larger mass. The outline of the bodies containing these two masses was faintly visible with the stain. They existed in large number in the spleen cells. In Major Leishman's opinion the bodies were residues of trypanosomes.

In July, 1903, Captain Donovan,[6] I.M.S., reported having found the same bodies in autopsy spleen smears from three consecutive cases said to have died of chronic malaria in Madras. Later he recovered them from the spleen of a boy suffering with an irregular fever.

Marchand and Ledingham[7] published in 1904 an account of a case of kala-azar[2] in a German soldier who had become infected while with

5. Leishman, W. B.: Brit. Med. Jour., 1903, i, 1252; 1903, ii, 1376; 1904, i, 303.

6. Donovan, C.: Brit. Med. Jour., 1903, ii, 79, 1401; Indian Med. Gaz., 1904, p. 321.

7. Marchand and Ledingham: Ztschr. f. Hyg. u. Infections—krankh., May, 1904.

his regiment in China and who died in Leipsic. Marchand observed the bodies in the tissues in this case late in 1902 or early in 1903.

Ronald Ross[8] has contributed to our knowledge of kala-azar and the Leishman-Donovan body, and has named the latter *Leishmania Donovani*, believing it to belong to a new genus of *Sporozoa*.

Laveran[9] examined Donovan's preparations and placed the organism with the *Piroplasmata*, calling it *Piroplasma Donovani*.

Strong[10] in 1906 described an intracellular body found in a tropical ulcer in Manila; that body may belong to the group described here.

The zoologic status of the Leishman-Donovan body was more closely defined by Leonard Rogers,[11] who succeeded in cultivating the body in citrated blood from a spleen puncture in the cold. The bodies became flagellated. Rogers' cultural work has been confirmed by Christophers.[12]

Captain Patton,[13] I.M.S., has made the highly important observation that developing Leishman-Donovan bodies in all stages may be found in infected bed-bugs, *Cimex rotundatus* (*C. macrocephalus*). He has also added to our knowledge of flagellates resembling the Leishman-Donovan body by his researches on *Herpetomonas* parasitic in insects. Captain Patton[14] has shown that a herpetomonas of *Culex pipiens* has a stage exactly similar to the human stage of the parasite of kala-azar, and another herpetomonas[15] in the Lygard bug, *Lygaeus militans* (Fabr.), which is almost identical with the parasite of kala-azar. This parasite passes its complete cycle in the intestinal tract of the bug.

On December 5, 1905, I performed an autopsy[16] on a negro Martiniquan, who had died at Ancon Hospital, Canal Zone, Panama. On examining smears from a peculiarly white atypical tubercle in the lung and from the spleen, liver and bone marrow I observed an intense invasion of large endothelial-like cells by small round or oval micro-organisms.

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8. Ross, Ronald: Brit. Med. Jour., 1903, ii, 1261 and 1401; 1904, i, 1049.

9. Laveran, A., and Mesnil, F.: Compt. rend. Soc. de biol., Par., 1904, cxxxvii, 95; cxxxviii, 187.

10. Strong, R. P.: Philippine Jour. Sc., 1906, i, No. 1.

11. Rogers, Leonard: Lancet, London, July 23, 1904, ii; Quart. Jour. Micros. Sc., November, 1904, xl.

12. Christophers, S. R.: Scientific Memoirs by the Officers of Medical and Sanitary Departments of the Government of India, Calcutta, 1905, new series, No. 15.

13. Patton, W. S.: Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India, new series, Nos. 27 and 30.

14. Patton, W. S.: Brit. Med. Jour., 1907, ii, 78.

15. Patton, W. S.: Personal communication to appear in Arch. of Parasitenkunde.

16. Darling, S. T.: Jour. Am. Med. Assn., 1906, xlvi, 1283

The bodies had definite refractile peripheries and their internal structure was not uniform or homogeneous. They were about three microns in diameter.

This was the first time in the New World that an organism of this type had been found responsible for a fatal infection in a native of the New World; and, so far as I have been able to learn, the organism described here and in two preliminary reports has never been seen or described before. Maj. Ronald Ross regards it as a protozoan organism, resembling somewhat the Leishman-Donovan body, but differing from it chiefly in not containing the chromatin rod usually seen in the Leishman-Donovan body. Wright's *Helcosoma tropicum* was obtained from a native of the Levant, recently arrived in Boston.

ACCOUNT OF THREE CASES.

CASE 1.—*Patient.*—C. D., Hospital No. 7715. Negro from Martinque, aged 27; occupation carpenter; residence, Paraiso, a village in the Canal Zone.

History.—The patient had been a resident of the zone three months. While in Martinique he had suffered from some mental disturbance. His present illness dates from Sept. 15, 1905, when he complained of fever and vomiting.

Condition on Admission.—On entering Ancon Hospital Dec. 5, 1905, mildly delirious and incoherent. Lungs clear. Abdomen scaphoid. Spleen enlarged. Blood: negative for malarial parasites; leucocytosis 2,200; hemoglobin, 60 per cent. (Dare's). Feces negative. Temperature: On admission, Dec. 5, 1905, 12:30 p. m., 101; pulse 120. December 6, 8 a. m., temperature, 95; pulse, 96. 4 p. m., temperature, 98; pulse, 100.

Autopsy.—The patient died December 6, 11:30 p. m. The autopsy was made on December 7, 8:30 a. m.

Macroscopic and Microscopic Examination.—Body of negro, moderately emaciated; length, 5 feet, 8¾ inches; inter-nipple distance, 7 3-16 inches; rigor mortis was plus. The odor on opening the thorax was suggestive of pulmonary tuberculosis. The right and left pleura were free. There were numerous red blotches (ecchymoses) beneath the visceral pleura of both lungs, 8 mm. in diameter. Many small nodules could be felt under the visceral pleura. The lungs on section were found studded with pale gray hyaline miliary tubercles from 2 to 3 mm. in diameter. The lungs were heavier and more voluminous than normal. The tubercles were not as closely packed or as numerous as is often found in miliary tuberculosis, and the general color of the lungs was bright red. The peribronchial lymph nodes contained a few small soft recently caseated tubercles. The nodes were enlarged and pigmented. The heart was small and normal. The liver was enlarged and pale, and there was slight atrophic cirrhosis. The spleen was enlarged to three times the normal in size; the pulp was very firm. The Malpighian bodies were distinct. Here and there were a number of small yellow nodules resembling tubercles. In the kidneys there were a few depressions in a cortex diminished to 8 mm. in depth. The pancreas and bladder were normal, and the rib bone marrow normal and dry. Examination of the brain showed the pia-arachnoid slightly edematous and more generally adherent to the cortex than normal. The calvarium was very thick. Several specimens of *Tricocephalus dispar* were found in the cecum. There were a few small superficial circular ulcers from 2 to 4 mm. in diameter in the cecum and ileum. The mesenteric lymph nodes and those at hilum of the spleen were enlarged and pale.

Bacteriologic Examination.—Spleen smears were negative for malarial parasites or pigment. Oval and round bodies were free in the plasma. In the rib bone marrow smears, there were traces of intracellular malarial pigment. A number of bodies similar to those in the spleen were seen. In lung smears tubercle bacilli were absent. There were myriads of intracellular and extracellular bodies similar to those found in the spleen and the marrow. A moist coverslip preparation from the intestinal ulcers showed motile amebas.

Anatomic Diagnosis.—Acute miliary tuberculosis, pulmonary type. Tuberculous lymphadenitis, peribronchial. Chronic interstitial splenitis. Atrophic cirrhosis. Chronic interstitial nephritis, slight. Lymphadenitis, mesenteric. Chronic leptomeningitis. Edema of pia-arachnoid. Ulcerative enterocolitis. Amebiasis. General infection by protozoon.

The micro-organism was not discovered in smears until later in the day, after the anatomic diagnosis had been made.

Appearance of the Parasite in Smears.—Lungs: This specimen was stained by carbolfuchsin and Gabbet's methylene blue, overstained with polychrome methylene blue, and differentiated with eosin. The polychrome blue was prepared as follows:

	gm.
Methylene blue, pure medic. Grüb	1.
Sodium carbonate, pure	.5
Distilled water	100.

This was placed in the thermostat one week, and kept at room temperature for six months. The excess of blue was removed by washing the smear alternately with alcoholic solution of eosin (0.5 per cent. in 60 per cent. ethyl alcohol) one second and distilled water a few seconds, until the internal structure of the parasite showed plainly. The parasite was oviform or round and was surrounded by a clear, refractile, non-staining rim, in thickness about one-sixth the diameter of the parasite. This refractile rim was present in all smears, whether previously treated with acid blue or not. The structure was not homogeneous, but consisted of a faintly staining substance and a deeply staining one; a clear space or spaces; and chromatin granules. The chromatin granules were generally single; sometimes two or more were counted. One large parasite appeared to have six such dots of chromatin. The granules were often situated in a clear non-staining zone at one side of the darker staining substance; at other times they were situated on the margin or within this substance, and also frequently appeared in the clear refractile capsule. The chromatin granules were generally dot-shaped, very rarely elongated. Occasionally two chromatin dots placed together simulated a rod form.

The clear space or spaces resembled vacuoles; at times they resembled the clear non-staining spaces seen in filaria embryos and trypanosomes. The staining substance almost entirely filled the capsule or refractile rim of the parasite. The circular contour of the staining substance was at times broken on one side by the clear non-staining zone. This zone varied in shape, size, and in its relation to the staining substance, being circular, oval, or irregular in form; being three-fourths the size of the entire parasite, or at times barely perceptible on account of its minuteness; being centrally located or eccentric; and being single or multiple—two or three.

In size the parasites were from one to four microns through their greatest diameter; commonly this diameter was three microns.

The parasite appeared to divide by fission into two equal or unequal elements. One parasite appeared to be dividing into four equal elements. Several parasites with chromatin dots scattered through their substances appeared as presegmenting bodies, ready to divide into five or six elements. Occasionally a smaller para-

site might be seen close beside a larger one, as though separating from it; the smaller one being about one micron in diameter.

Although oval or round in outline, the staining substance, together with the clear, non-staining zone and chromatin granules, gave a varying picture, depending on the point of view. Forms suggesting the appearance of familiar objects, such as the eye, a shield, a conch shell, a bullet, or a shuttle, were seen. The resemblance of the deeply staining substance in certain parasites to a mammalian embryo in "fetal attitude" was very striking.

In the lung smears the parasite was apparently always intracellular and the cells contained from ten to one hundred or more parasites. The appearance of free parasites was probably due to the squeezing and breaking up of infected epithelial cells by pressure in making the smear. One unbroken alveolar epithelial cell occupied one-third the diameter of the field (1/12 oil im. No. 1 oc. B. & L.). Parasites had invaded the cell nucleus as well as the cytoplasm, and it was estimated that this cell contained more than three hundred.

Spleen and rib marrow smears showed fewer parasites, two or three to a field, and they appeared to be extracellular. The nucleus of a spleen or marrow cell appeared now and then to have been invaded. Each parasite had a definite refractile rim, as in the lung smears, and its internal structure could be well made out. Red blood corpuscles were never invaded.

Three flagellated forms were seen in a lung smear. The distal extremity of one of the flagella contained a rod of chromatin placed at right angles to the flagellum, simulating the relation of centrosome to chromatin filament in *Trypanosoma Lewisi*. The flagella were single, short and thick, without chromatin filaments, and were enclosed by the refractile capsule, continuous with that of the body of the parasite.

Examination of Sections.—Sections were fixed in Zenker's solution and stained by eosin and hematoxylin, Van Giesen's method, and polychrome-methylene blue.

Lung: The alveolar capillaries were tortuous and engorged with red blood corpuscles. In places the walls were broken down, stretched, or greatly distended. No leucocytes were seen within the capillaries. The epithelial cells of the alveolar walls was desquamating or completely shed. The alveoli were seen to be filled with red blood corpuscles, generally having a washed-out appearance; red blood corpuscles and serum; or red blood corpuscles, serum, and large swollen alveolar epithelial cells containing many parasites.

Polymorphonuclear leucocytes were rarely observed in the alveolar contents; a few mononuclear elements were noted. There were no tubercles. The pseudo-tuberculous areas were made up of alveoli with broken, distorted, or collapsed walls, containing many alveolar epithelial cells, distended by parasites. Small vessels or capillaries were seen to pass through the pseudo-tubercles, but there were no evidences of the hemorrhages seen in other alveoli. Within these areas there were enormous numbers of parasites generally contained within epithelial cells—rarely free. The nuclei of invaded cells stained well, though often more faintly than normal. The cytoplasm of badly infected cells was wanting, and there were numerous distended epithelial cells devoid of cytoplasm and parasites. The infected cells had a distinctly staining rim of cytoplasm, even when their nucleus and cytoplasm was gone.

Liver: There were numerous faintly staining areas ranging in size from that of a single liver cell to those one-third the size of a lobule; in which the liver cells and endothelial cells of the portal capillaries were completely transformed by invading parasites. In the larger areas the cytoplasm and nuclei of the invaded cells had disappeared or did not stain. There was a mass of débris, embedded in which were myriads of parasites. In places the liver cells were normal; in others they had suffered cloudy change. In these latter localities

there appeared to be a stasis of blood in the portal capillaries due to occlusion of capillaries by enormously distended endothelial cells filled with parasites.

There was a distinct primary invasion of liver cells in places, although oftener it seemed that many liver cells became invaded after they had had their nutrition cut off by infected overlying endothelial cells.

Around the portal space the connective tissue was increased in amount and there was a recent round cell infiltration. The bile ducts and their epithelium were normal.

Spleen: The splenic spaces were greatly engorged with red blood corpuscles. The connective tissue was moderately increased, its cells were swollen, cloudy, and at times contained parasites. There was cloudy swelling of mononuclear cells in small areas here and there, and many of these cells contained parasites. There were also numerous free parasites.

Lymph Node from Hilum of Spleen.—The cortical follicles and medullary cords of the dense lymphoid tissue were, with the exceptions noted below, normal. The capsule and reticulum throughout the node were the seat of degenerative changes. The reticulum of the loose lymphoid tissue enclosed many large mononuclear cells possessed of distinctly staining nuclei, and contained many parasites.

There were two cortical follicles, and portions of a medullary cord which had undergone cloudy swelling and necrosis, amid the débris of which were mononuclear cells containing parasites. The margins of these areas showed beginning degenerative changes; many fragmented nuclei were seen, as well as mononuclear cells distended by parasites.

Peribronchial Lymph Node.—This node contained several old fibrocaseous tubercles, and one giant cell. The reticulum and capsule of the node were greatly thickened in places. A lymph vessel beneath the capsule contained mononuclear cells infected by parasites.

CASE 2.—*Patient.*—G. B., Hospital No. 9141. Negro from Martinique; aged 29; occupation, laborer; residence, Corozal, a village in the Canal Zone. The patient complained of headache, vomiting and diarrhea. It was not known how long he had been ill or how long he had been a resident of the Isthmus. He presented a wasted appearance. His visible mucous membranes were pale. His spleen was palpable and his thorax negative. He was admitted to the hospital Jan. 9, 1906. Malarial parasites were present in his blood.

Clinical Course.—During the first week after admission the temperature was irregularly continuous, being about two degrees above normal. During the second week the temperature curve became regularly remittent; physical signs of pneumonia on the right side were apparent. On January 29, the day of his death, it was noted that the liver extended two finger's-breadth below the costal margin. The spleen extended to a similar depth and both spleen and liver were tender. The patient was conscious and coherent, and complained of pains in his legs and thighs. He lay on his back with his thighs flexed and complained of burning sensations in his feet. His calves were tender on the slightest pressure and his patellar reflexes were absent.

Autopsy.—This was made Jan. 30, 1906, 8 a. m., four hours after death. The body was 5 feet 7 inches in length and much emaciated. Rigor mortis was plus. Pleura free—negative. Peribronchial lymphnodes enlarged. Pericardium, negative. Omentum contracted. No peritonitis noted. Lungs: The upper part of the lower lobes showed patches of bronchopneumonia. The upper lobes were negative. Heart: Small, flabby. Right heart considerably dilated. Valves negative; muscles light in color. Liver: Normal in size; color reddish brown. Adrenals: negative. Kidneys: Somewhat enlarged. Their capsules stripped with ease and both were much congested. Spleen: Five times its normal size, firm. There was an increase in its fibrous stroma. Its pulp was deep brown in

color and smears contained æstivo-autumnal malarial parasites. Intestinal tract: The stomach contained considerable quantity of coffee-ground material and the mucosa, while very pale, showed no indications of hemorrhage. The intestines contained round worms, whip-worms, and New World uncinaria worms.

Anatomic Diagnosis: Bronchopneumonia; acute parenchymatous nephritis; uncinariasis; ascariasis tricocephaliasis; malarial fever, e. a.

Smears from the spleen, bone marrow, liver and lymphnodes examined the following day showed numerous micro-organisms similar to those seen in Case 1.

Histopathology.—Kidney: The convoluted tubules were generally distended. The nuclei of the epithelial cells were swollen and did not stain deeply. Here and there a nucleus was missing. The lumen contained coagulated albumin and an occasional desquamated epithelial cell. Some of the straight tubules contained hyaline casts. The epithelium of the convoluted tubules was generally flattened, not cuboidal. The convoluted tubules were widely separated by a cellular exudation or proliferation. The cells making up this exudate or proliferate had eosin-staining protoplasm and most of them had deeply staining nuclei, eccentrically placed. Minute hemorrhages were also noted in these interstitial places. The cells of the glomeruli and of Bowman's capsule were swollen and their nuclei were swollen and pale. A few convoluted tubules showed colloid degeneration. The vessels appeared normal. Heart and pancreas: Negative. Spleen: The splenic spaces were distended by red blood cells. Numerous mononuclear phagocytes containing malarial pigment were seen. A few of these phagocytes were dotted with parasites. The Malpighian bodies showed some disappearance of their lymphoid elements. Liver: There was a slight round-cell proliferation, around the portal spaces and in small foci here and there. The columns of liver cells everywhere appeared flattened and attenuated, but the capillaries were not engorged. There appeared to have been a diffuse disappearance of liver cells. There were some very small areas about the size of a dozen liver cells in which there was an almost complete disappearance of liver cells; the space being occupied by endothelial cells containing malarial pigment and occasionally parasites. Throughout the section there was much malarial pigment enclosed within endothelial cells lining the capillaries. Many of these endothelial cells were distended by parasites (*Histoplasma capsulatum*) as well as pigment. From this section the earliest lesion was apparently that in the endothelial cell. The areas of round-cell proliferation—apart from those around the portal spaces—were frequently associated on one side by the small areas of necrosis containing parasites. Some of these areas of necrosis extended outward from a portal space; others were in the intermediate zone; while others could not be oriented on account of the obscuration of the lobule outline. One of these small areas, where the liver cells had disappeared, contained a typical giant cell with a mural arrangement of its neuclei on one side. This giant cell was in the intermediate zone of a lobule. The giant cell was not a part of a tubercle, and around it were no round cells, epithelioid cells, or nuclear fragmentation. The structures in the portal spaces were normal. In this instance the infection was a mixed one of the malarial parasite and *Histoplasma capsulatum*. Adrenal: Negative. Lung: The capillaries were tortuous and engorged with red blood cells. The alveoli contained red blood cells and polymorphonuclear leucocytes in about equal numbers, also a few desquamated alveolar epithelial cells. No parasites were seen. Lymph Node: The spaces of the lymphoid tissue contained numerous large mononuclear phagocytes—some with double nuclei—many of which had engulfed red blood cells. There were no areas of necrosis, the changes being hyperplasia of large and small lymphoid cells. No parasites were seen in the section.

Drawings showing various specimens of *Histoplasma capsulatum* from the spleen of Patient 3 (× 1000).

CASE 3.—*Patient.*—Fu Mas; Hospital No. 17,184; aged 55; a native of Canton, China; admitted to Ancon Hospital, Aug. 9, 1906.

History.—From his closest friend the information was obtained that the patient came direct from Canton, China, to the United States. He had been living on the Isthmus during the last fifteen years, living at Bocas del Toro, near Colon, four or five years of this period. About six months before he died he was employed in a little shop near the hospital buildings at Miraflores. He had lived there five months when he removed to Panama one month before his death. His friend said that the patient had been going down hill physically for the five months preceding his death, that he had had fever, chills, slight emaciation, and that no dysentery or cough had been noticed. There had been no pigmentary changes of the skin or changes in the hair noticed, and so far as he knows there was no bleeding of the gums, but there had been some loss of strength.

Clinical Course.—His temperature on admission was 102, falling to 97.5 the following morning. His pulse ranged from 98 to 120 and the respirations from 18 to 30. The hemoglobin was estimated at 70 per cent. His blood was otherwise negative. In the afternoon of August 10 involuntary urination was noticed. The patient was said to have been in a peculiar coma, and slept all day, but could be aroused. Died, Aug. 10, 1906, 11:05 a. m.

Autopsy.—Aug. 11, 1906, eighteen hours after death. Body of male Chinese. Hair cropped short. Moderate pitting of feet, legs, thighs, lower abdomen and left side of face, which latter was congested. Rigor mortis was absent. There were three or four raised recent broad papules 8 mm. in diameter on the left arm, outer aspect. External genitalia normal. Scrotum not edematous. Subcutaneous tissues slightly edematous. Muscles of chest, abdomen and legs very pale. Sartorius muscles a dull gray color. The knee joints normal. Lungs: Voluminous and the pleura free. Right and left upper lobes and middle lobe contained a few raised hyaline dense areas resembling tubercles. They were from 2 to 6 mm. in diameter and were often irregular in contour and elongate. They were always surrounded by a raised hemorrhagic zone about 4 mm. in thickness. The peribronchial lymph nodes were slightly enlarged, pigmented black, and contained no tubercles. Pericardium normal, containing about 30 c.c. clear fluid. Heart: Rather small and flaccid; valves, normal; musculature dull brown color. Liver: Enlarged, capsule smooth. Organ presented a unique appearance, due to a grayish yellow arborescence. The limbs of the arborescence were 4 mm. in diameter and apparently followed portal radicals. Their centers were gray, their peripheries rather yellow. The areas contained only four or six limbs, but were scatttered thickly throughout the entire organ, save in one portion of the liver near the falciform ligament about 16 c.c. elongate anteroposteriorly. There was much fatty infiltration of the parenchyma. The gall bladder was normal. The portal lymph nodes were enlarged, pale, yellow, slightly edematous and friable. Spleen: Enlarged, long and relatively narrow; its pulp was firm, friable and dark red in color. Malpighian bodies indistinct. Capsule smooth and tense. Kidneys and Adrenals: Negative. The peritoneal surface of the sigmoid flexure, descending colon and perirectal peritoneum near Poupart's ligament was intensely pigmented black in spots. Aorta: Normal. Testes: Normal. The colon contained about twenty-four small 6 mm. round pigmented areas of hyperplasia and ulceration. Small Intestines: The entire ileum and lower two-thirds of the jejunum contained altogether about 50 circumscribed areas of hyperplasia infiltration, necrosis, ulceration and hemorrhage. There were several stages to the process. 1. A pigmented raised area five to six mm. without ulceration. 2. The same with much infiltration of periphery. 3. Necrosis. 4. Recent ulceration with fresh blood clotted on the surface of the ulcer (8 mm.). 5. A puckered, pigmented scar 8 mm. in diameter. The mesenteric lymph nodes were not appreciably enlarged. The postperitoneal lymph nodes were enlarged

and were similar to the portal nodes. The upper jejunum, duodenum, stomach and esophagus were normal. The calvarium was thin and the cranium markedly brachycephalic in type. Brain: Pale, normal. Accessory sinuses; normal. Smears from liver, intestinal ulcers and spleen, contained many histoplasma bodies.

Cause of Death.—Protozoon infection—histoplasmosis.

Histopathology.—Kidney: There was some edema. The epithelium of the convoluted tubercle was swollen and in places desquamated and cloudy. Most of the nuclei failed to take the stain. Many of the tubules contained granular débris, desquamated epithelium and occasionally a hyaline cast. There was a slight increase in the intertubular connective tissue and in Bowman's capsule. The space between the glomerulus and Bowman's capsule frequently contained a large amount of coagulated albumin.

Liver: The section showed extensive destruction of the parenchyma by coagulative necrosis having a reticulated character; and the replacement of these areas of necrosis by connective tissue, old and newly formed. The cells of the latter showed an extensive invasion by the micro-organism; many of the cells contained thirty or forty parasites. The process was so extensive that a zonal arrangement could not positively be made out. The older and more extensive areas of necrosis and replacement appeared to be in the portal spaces, where the areas of connective tissue were frequently broader than a liver lobule. The areas of coagulative necrosis varied in size from two or three liver cells up to one-half the diameter of a lobule. These areas of necrosis were scattered everywhere; sometimes isolated, at other times on the margin of a large area, which had apparently undergone necrosis and been replaced by connective tissue. There did not appear to be a shrinkage in this substitutive fibrosis, and there was apparently no distortion of the liver lobule. The areas of necrosis always contained parasites; some parasites appeared to be free, others were enclosed in large vesicular cells, resembling endothelial cells. The heaviest invasion by parasites was in the connective tissue cells, which had replaced the areas of necroses, and these areas corresponded to the hyaline opalescence noted at autopsy. The connective tissue of the capsule of the liver was thickened and frequently communicated with the infected underlying areas of necroses, but the capsule showed no invasion by parasites. The hepatic vein occasionally was surrounded by connected tissue which had been invaded by parasites. The epithelium of the bile ducts showed no appreciable proliferation and its epithelium was not invaded by parasites.

Ulcer, Ileum: The peritoneum and muscle wall were normal. The mucous membrane was pushed away from the muscle wall by an oval mass of large round and oval cells, most of which had a large amount of eosin-staining cytoplasm, which was more or less replaced by micro-organisms. The periphery of this granuloma, nearest the lumen of the intestine, was denuded of mucous membrane, almost to the depth of the muscularis mucosa. Under the higher power there was seen to be an extraordinary invasion of certain cells in the granuloma by the micro-organism. The nucleus of the invaded cell was either eccentric, or pushed to one side and the micro-organism was closely packed in a clear achromatic space. This achromatic space had no definite membrane and was surrounded by eosin-staining cytoplasm of the cell. Some of the invaded cells did not show this achromatic space, but merely showed a mass of micro-organisms embedded in the cytoplasm of the cell. In this section the blood vessels were not involved, but the lymph spaces everywhere showed an invasion of their lining endothelium by parasites. While most of the micro-organisms were intracellular there was quite a large number apparently free. The epithelium of the tubular glands was everywhere free from an invasion by micro-organisms, yet the interglandular connective tissue stroma and the basement membrane were

crowded with parasites. The denuded surface of the ulcer was rich in infected cells and there were detached cells and parasites lying free on the surface. The morphology of these free parasites on the surface was the same as those embedded in tissue. Flagella apparently were not present. The cells making up the granuloma were generally large, with small and deeply staining, or large and vesicular nuclei; most of them had a large amount of eosin-staining cytoplasm, while others had a slight affinity for hematoxylin. This section showed a more intense invasion by the parasite than that of any other tissue. Epithelial cells, blood vessels and smooth muscle were not invaded. In this tissue the micro-organisms had spread along the lymph spaces. A peribronchial lymph node showed several large areas in which the lymphoid tissue of the node has been replaced by dense fibrous tissue, in the periphery of which there was a good deal of black pigment. Here and there where the lymphoid tissue still remained there were large cells, sometimes appearing to be a part of the reticulum, at other times endothelial cells bulging out into the lymph spaces, packed with parasites.

Spleen: The splenic spaces were greatly distended by red blood cells and there was a very striking absence of leucocytes in the splenic spaces. The reticulum did not appear to be increased in amount by the proliferation of its elements, but there was an extensive invasion of large cells in the reticulum by parasites, and there was also an invasion of endothelial cells lining the splenic spaces by parasites; on the whole, however, the most extensive invasion was that of cells making up the reticulum of the organ. There was an almost complete disappearance of the lymphoid cells of the Malpighian bodies, the reticulum of which was thickened and fibrous.

Lung: Section of granuloma 2.5 mm. in diameter. The pulmonary alveoli surrounding the granuloma were full of red blood cells. The granuloma consisted of a reticulum conveying small blood vessels. The reticulum was not alveolated but consisted of whorls and strands of loose, connective tissue, small blood vessels, and what appeared to be the remains of alveoli, filled with very large cells, containing micro-organisms. In places there were alveoli partly collapsed, containing very large cells with single or double nuclei; these cells showed an enormous invasion by parasites. Some of the cells must have contained from two hundred to three hundred parasites. The alveoli also contained red blood cells and desquamated epithelial cells, containing both parasites and pigment (dust cells).

PARASITOLOGY.

What is the position of the micro-organism in the zoologic scale? From its morphology, staining characteristics, and the presence of a few flagellated forms, it is regarded as a protozoon having a flagellated phase.

During some microscopic examinations of tropical surface waters, the water was collected in several flasks which were placed on shelves near a window, sealed with paper and cotton to keep dust out, and examined from time to time for the development of flagellates. Most of the flagellates were of the cercomonas type; others had a vibratile short anterior or posterior end near which was located a small refractile dot of chromatin. Opposite was the flagellum, near which was to be found the larger refractile globule of chromatin.

A sample of water collected July 12, examined August 20, contained a thick surface pellicle having a very disagreeable odor. The pellicle contained numerous radiate colonies of minute cultural forms (*colonies radiées*) and fewer larger oval flagellated forms, having a macronucleus, micronuclear dot, and a short, thin flagellum. Three or four chromatin dots were to be seen occasionally along the periphery of the body. The other samples, collected June 30, examined August 20, contained among other forms an oval non-flagellated body strikingly like the Leishman-Donovan body. Its size was somewhat larger than the Leishman-Donovan body as it is seen in tissues, but the chromatin rod and macronucleus were present. The macronucleus being in the center of the body and the chromatin rod near the periphery between the macronucleus and the pointed end of the body. Between the macronucleus and the broad end of the body was a small oval vacuole.

When these bodies were stained by the intra-vitam method, using gentian violet, or methylene blue, both refractile bodies became stained before the surrounding cytoplasm was tinted. The flagellates remained motile for some time after their centrosomes were stained, then the entire body became spherical and motionless, instead of oviform. These bodies were not cultivable on ordinary laboratory media or in sterilized tap water.

Attempts have so far been unsuccessful in finding in water pellicles a body having the characteristics of *Histoplasma capsulatum*.

In August I learned that Ross,[17] Novy[18] and others had found flagellates parasitic in mosquitoes and fleas. On searching for flagellates in larvæ and adult mosquitoes, I found a few resembling those found in water pellicles.

One larva, *Culex*, three-fourths grown, examined Aug. 30, 1907, contained within a flat-celled body cavity, several oval flagellates with short flagella, having a single refractile dot.

There can be no doubt whatever that protozoa related morphologically to the Leishman-Donovan body can be found in the surface pellicles of tropical waters and in the intestinal tracts of insects, for many of the latter in the larval stages, or in feeding, come into contact with water more or less rich in aerotactic flagellates. The search has been continued for protozoa having a resemblance to the micro-organism described here, by making examinations of most of the animals coming to the laboratory. They include calves, iguanas, raccoons, monkeys, rats, mice, snakes,

17. Ross, R.: Jour. Hyg., 1906, vi, 96, 97, 101-108.
18. Novy, MacNeal and Torrey: Jour. Infec. Dis., 1907, iv, No. 2.

marsupials, besides various insects. The feces or intestinal tracts are collected, examined and kept for cultivation. The nearest approach to an organism having a morphology resembling that of the *Histoplasma capsulatum* was one seen in some bloody mucus obtained from the inflamed colon of a rat, killed in the laboratory court-yard, April 14, 1908. In this rat protozoon the cytoplasm stains faintly blue. Its outline is round or oval. It contains frequently, two vacuoles, oval in shape, and an open diamond-shaped or irregularly circular granular chromatin ring from which three pair of flagella about twice the length of the micro-organisms are given off, three flagella on each side of the apex of the body. Opposite this, occasionally a single pair of flagella may be seen, similar in length and staining characters to the other pair, viz., eosin-staining and twice the average length of the body. These protozoa are not encysted or encapsulated. Diameter is six microns. They are mildly suggestive of *Histoplasma capsulatum* and very strongly impress one that *Histoplasma capsulatum* has during its flagellate phase several flagella given off from that portion of the body nearest to the clump of chromatin.

SUMMARY.

The clinical notes are very brief, as none of the cases were diagnosed during life.

The most striking clinical features are the splenomegaly, emaciation, irregular remittent temperature and leukopenia.

The patients were men. Two were Martiniquan negroes, the third case was that of a Chinese, who had been a shop-keeper on or near the Isthmus of Panama for fifteen years.

Their local residences were Mariflores, Paraiso and Corozal, small villages on the Pacific slope of the Isthmus, along the line of the Panama Railroad. The Martiniquans were laborers.

Histoplasmosis is not at present encountered. Three cases have entered and died in Ancon Hospital out of thirty-three thousand admissions. This covers a period of about three years.

The greatly improved hygienic condition of laborers throughout the zone has no doubt favored the arrest of the progress of the infection.

Nothing is known about the hygienic condition in which the patients were living.

The cases undoubtedly originated either in Martinique or on the Isthmus of Panama. The Chinese had been living continuously on the Isthmus and at Bocas del Toro, near Colon, for fifteen years.

It would be difficult to determine the influence of season, as the duration of the disease is not definitely known. Patient 1 died in December at the end of the rainy season; patient 2 died in January at the beginning of the dry season; while patient 3 died in August at the middle of the rainy season.

Postmortem changes were delayed. The body of the Chinese was examined seventeen and one-half hours after death, yet the postmortem changes usually seen in bacterial infections were absent. Subcutaneous tissue was diminished and slightly edematous in case 3. There were numerous subpleural (visceral) ecchymoses in case 1. The ecchymoses corresponded to and overlaid pseudo-granulomata in the underlying parenchyma. There was stellate cicatricial thickening of the pleura over an area of granulomatous tissue in the right lung in Case 3.

In the lungs were disseminated hyaline pseudo-granulomata in Cases 1 and 3. These hyaline areas were round or irregular in shape, pearly white and dense. They were 2 to 3 mm. in diameter when discrete. The irregularly shaped areas were 6 to 12 mm. in diameter. These pseudo-granulomata were always surrounded by raised areas of hemorrhage about 4 mm. wide. There was a terminal bronchopneumonia in Case 2.

The peribronchial lymph nodes, while enlarged and pigmented, did not show the same amount of enlargement noticed in lymph nodes draining the liver and spleen.

The heart was smaller than normal and its size corresponded with the general atrophy of voluntary muscles.

The liver was enlarged in Cases 1 and 3. Case 3 presented a diffuse arborescence, the limbs of the arborescence being about 4 mm. in thickness, having gray centers and yellow peripheries. These areas corresponded to necroses with infiltration by parasites. The capsule was smooth. The portal lymph nodes were enlarged, pale, yellow and friable.

The enlargement of the spleen was marked. The capsule was tense and the pulp firm, yet friable, and dark red. The Malpighian bodies were distinct in Case 1 and indistinct in Case 3. On removal, the spleen was rigid and retained its original form; it was not flexuous. The lymph nodes draining the spleen were similar to those draining the liver.

The pancreas, kidneys, bladder, ureters and genitalia were negative.

The ileum, jejunum and colon were the seats of a process that appeared first as a circular raised pigmented granuloma in the mucosa. The infiltration increased at the periphery and later a small circular ulcer appeared, 8 mm. in diameter. Still later a pigmented puckered scar was noted. One of the ulcers in Case 3 was covered with recent blood.

The duodenum, upper jejunum, stomach and esophagus were normal.

The mesenteric lymph nodes were not appreciably enlarged.

The postperitoneal lymph nodes were enlarged, pale and friable.

The peritoneum covering the rectum, sigmoid flexure and the parietal peritoneum near Poupart's ligament was intensely pigmented black in spots.

The brain and rib marrow were negative, and the accessory nasal sinuses normal.

The micro-organism was found in endothelial cells lining blood and lymph vessels and in areas of necrosis and pseudo-granulomata, in the intestinal tract, spleen, liver, lungs, lymph nodes and rib marrow.

The bodies are round and oval. There is among the larger forms a tendency toward an oval outline. An average-sized spherical body is 3 microns in diameter. The longer diameter of an oval body is 3.75 microns. The bodies are always surrounded by a clear, refractile, achromatic zone or capsule, giving the impression at once of an encysted protozoon. The body does not stain homogeneously, but very irregularly, hardly any two parasites looking exactly alike. The body consists of a deeply staining substances, or chromatin, a faintly staining substance staining light blue with polychrome stains; and achromatic spaces. The deeply staining substance, or chromatin, is practically always heaped up along one end of the body; sometimes it consists of a single mass or several small masses of chromatin; sometimes it is ring-shaped or occasionally extending along half of the periphery of the body, being crescent-shaped. Occasionally a chromatin dot or very rarely a chromatin rod will be seen near the larger chromatin body. This chromatin dot or chromatin rod may sometimes be at the opposite end or side of the body. There may be several such dots of chromatin. When there are several of good size the bodies appear to be in a presegmenting stage. The faintly staining blue substance takes up the rest of the space, excepting where there may be one or two small achromatic zones, resembling the vacuoles of protozoa. These vacuoles are irregularly disposed, being sometimes in the center and at other times near the periphery of the body. The most striking thing about the parasite is the extremely irregular way in which the staining substance is disposed. This is in striking contrast with the appearance of the Leishman-Donovan body.

The micro-organism is a protozoon probably belonging to the *Flagellidia* and is probably related morphologically to small oval protozoa having several pairs of flagella in relation with the large chromatin mass.

This latter is suggested on account of certain morphologic analogies. Of course, it will be necessary to cultivate the micro-organism from splenic pulp obtained from a patient during life in order to determine its morphology in the flagellated stage.

The parasite always takes polychrome blue stains like a living organism. Twenty-four hours after the death of the host, the chromatin and faintly staining basophilic substance of the micro-organism stains beautifully. Under similar conditions the malarial parasite would not stain so well. Occasionally in marrow smears the micro-organism requires prolonged contact with the stain, probably due to the resistance or impermeability of the refractile capsule. The portal of entry is unknown The disease may be transmitted by a suctorial insect or acarid, or the micro-organism may gain entrance to the tissues of the host through the intestinal tract.

Case 3 presented several cutaneous papules; Cases 1 and 3, small intestinal ulcers and granulomata. The intense invasion of the spleen and liver, of the lymph nodes draining these, and the presence of intestinal lesions, is strongly suggestive of an entrance through the intestinal tract —ileum or colon.

Cases 1 and 3 presented infected pulmonary pseudo-granulomata, while Case 2, which did not present so intense a general infection, showed no pulmonary pseudo-granulomata. The pulmonary lesions, therefore, may appear late. The micro-organism differs from the Leishman-Donovan body in having a more complex arrangement of its deeply staining substances or chromatin, of a lack of uniformity to the disposition of the chromatin and in not possessing a chromatin rod.

The disease caused by the micro-organism must be like kala-azar because of the corresponding splenomegaly, emaciation, irregular pyrexia and leukopenia.

The chief anatomic difference is the pseudo-granuloma in the lungs. I have found no reference to such a lesion in the records of East Indian autopsies.

In conclusion it should be said that this disease, although no longer seen in Panama, is probably to be found in unhygienic and less salubrious regions of tropical America, not yet disturbed by the sanitarian.

Up to the present, *Histoplasma capsulatum* has not been found in smears or sections of localized skin ulcers or granulomata. Reasoning from analogy it will be found, if not in Panama then in some other region of tropical or subtropical America. The researches of Captain James,[19] I.M.S., show that the geographical distributions of kala-azar,

19. James, S. P.: Scientific Mem. by Officers of the Medical and Sanitary Departments of the Government of India, Calcutta, 1905, new series, No. 13.

the general infection by the Leishman-Donovan body, and of Delhi or Oriental sore, the localized infection, are not the same. Oriental sore is common in Bagdad and the Punjab, the latitude of the former being about that of Charleston, S. C., or southern California, while kala-azar is endemic in Assam and Madras.

I wish to express my thanks to Colonel W. C. Gorgas, U.S.A., Chief Sanitary Officer, and to Major John L. Phillips, U.S.A., Superintendent of Ancon Hospital, for their kind permission to publish this report.

Ancon Hospital.

INFLUENZA AND INFLUENZAL PNEUMONIA.

THEIR ETIOLOGY AND COMPLICATIONS AND THE OCCURRENCE OF INFLUENZA BACILLI IN VARIOUS INFECTIOUS DISEASES.

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Influenza was little known, particularly from the bacteriologic viewpoint, before the pandemic of 1889-90. This, occurring at a time when bacteriology was making important contributions to medicine, naturally proved a fruitful field for research and resulted in the discovery by Pfeiffer of a bacillus (*Bacillus influenzæ*) which since then has been generally accepted as the causal organism. Many epidemics of clinical influenza have appeared since, and in some Pfeiffer's bacillus has been found, while in others a variety of organisms has been described. The idea is prevalent that every condition occurring in epidemics and giving the clinical picture of influenza is due to the influenza bacillus, and that if influenza bacilli are found in the respiratory passages in these conditions the diagnosis of influenza is justified.

One purpose of this paper is to call attention to conditions which the physician commonly calls influenza or grip, and with which the influenza organism in no way is concerned. The second is to describe the results of the clinical and bacteriologic study of a series of cases usually called influenzal or grip pneumonia. A third purpose is to point out the common occurrence of organisms of the influenza type in the respiratory passages in a great variety of diseases of infectious origin.

INFLUENZA OR GRIP.

Opportunity occurred to study bacteriologically cases of influenza occurring in epidemics of 1905 and 1908 in Chicago. Clinically they corresponded to influenza as it occurred, for instance, in the pandemic of 1889-90. On the whole, probably the disease was less severe, but many cases were followed by serious complications. The onset, as a rule, was sudden, often with a chill, followed by the usual symptoms of coryza, pharyngitis, cough, headache, backache, soreness in muscles, fever and prostration. The general conception among physicians was that of an infection with influenza bacilli.

My efforts were directed chiefly to a bacteriologic study of the secretions of the respiratory passages. Usually sputum was obtained and in many instances nasal secretions and swabs of the throat were also exam-

ined. Smears were made and stained by Gram's stain, counterstained with carbolfuchsin and also with methylene blue. Cultures were made of the washed sputum and of the nasal material on blood-agar plates. In most instances pigeon-blood was used in preference to human or other animal bloods, because of the more profuse growth of influenza bacilli in the former.

In the 1905 epidemic seventeen typical and severe cases of clinical influenza were examined. In only three could influenza bacilli be found, and in only one of these were they numerous. As a rule the sputum was obtained early in the disease, when the coryzal and pharyngeal symptoms were at their height. Compared with the normal bacterial flora of the throat, the results showed, on the whole, an increase in streptococcus colonies. The green colonies characteristic of the pneumococcus group were always present. *Micrococcus catarrhalis* was found in a number of instances; in no case during this epidemic was *Streptococcus mucosus* found.

The epidemic of 1907-08 was characterized by severity and wide prevalence. At one time it was estimated that nearly one-third of the people in the city were ill with the grip. A bacteriologic study of the respiratory secretions was made in twenty-four cases. Influenza bacilli were found in four cases only. Streptococci were found in every case; in most instances they were more numerous than in normal throats, as was found to be the case in the previous epidemic. In some cases they were very few in number. Pneumococci were always present and in large numbers. In some of the most severe cases, early in the disease when the clinical symptoms were at their height, pneumococci in almost pure growth appeared on the plates. In four instances *Streptococcus mucosus* was obtained and twice only the *M. catarrhalis* appeared.

In many of the above cases, examination of the secretions was made from time to time during the course of the disease with a view of determing the variability of the bacterial flora. In the four cases in which influenza bacilli were found, in no instance did they occur in the initial stage of the disease; only after several days or during the time when the acute symptoms abated and a persistent cough appeared, as frequently happened, did the bacilli make their appearance. In general this may be said of *Streptococcus pyogenes, Streptococcus mucosus* and *M. catarrhalis.* Early in the disease the bacteriology is much less complex than after several days. The pneumococcus appears to be the predominating organism in the acute stage. Then the other varieties mentioned appear to come in as secondary invaders, so that the stage of the disease should always be considered in interpreting the bacterial cultures.

As illustrating the above statements some examples may be cited briefly:

In a typical case of grip the patient complained of chill, fever, pain in legs, back, slight dryness and soreness of throat and malaise, and had abundant mucopurulent secretion from the nose and throat. On the second day cultures on blood-agar plates of material from the nasopharynx showed the pneumococcus colonies to make up about 80 per cent. of all the colonies, the remainder being hemolytic colonies of the streptococcus group. At this time no influenza bacilli, *M. catarrhalis* or other organisms were present. Five days later the more acute symptoms had abated, but there was still present malaise and marked mucopurulent secretion from the nose and throat. At this time there was observed nearly a pure growth of influenza bacilli on the plates and in the smears. Only a few green colonies and hemolytic colonies were obtained. Four days later, or approximately eleven days after the onset, examination of the discharge showed 80 per cent. of the colonies to be influenza bacilli, about 20 per cent. pneumococcus, and only an occasional streptococcus colony. On the nineteenth day the plates showed the pneumococcus colonies to be the most abundant, influenza bacilli nearly as numerous, and a few streptococcus colonies. On the thirty-fifth day after the onset there was a mucopurulent secretion from the nasopharynx, which had recently been increased by an acute exacerbation of the nasal and throat symptoms. Examination of the discharge showed again a predominance of influenza bacilli arranged in symbiotic relationship to other colonies; of the remaining colonies about 60 per cent. were pneumococci and 40 per cent. streptococci. The case is instructive in showing the early predominance of the pneumococcus organisms, the appearance of influenza bacilli about the end of the first week, their gradual disappearance with the abatement of the symptoms and the increase not only of these bacilli, but also of the streptococcus on the recurrence of acute symptoms. In another typical case in which marked nasal symptoms persisted for about three weeks, streptococci were found to be predominant, while no influenza bacilli were present.

Just as interesting as the above observations are those obtained in other cases in which the subsidence of symptoms was more prompt. Here the pneumococcus colonies were, as a rule, nearly pure early in the attack and continued the predominating organisms throughout, without the appearance of influenza organisms at any time and with little or no increase in streptococcus colonies. Some exceptional findings were observed in certain cases which deserve comment:

A young man became ill with the grip. Cough and purulent ex-

pectoration persisted, with feeling of malaise and indisposition. Opportunity was afforded to analyze the secretions at about the end of the third week. At this time the predominant organism was the influenza bacillus, showing symbiosis in relation to the pneumococcus and the few streptococcus colonies which were present. No other organisms in smear or culture were observed at this time. One week later, the symptoms having continued the same, another analysis of the sputum showed again influenza bacilli in large numbers, few streptococci and pneumococci relatively, and a small number of *Streptococcus mucosus* colonies. Two days later there appeared a fresh infection manifested by marked stuffiness of the nose, increased cough, lacrimation, dryness of throat, etc. From the glairy mucus from the nose and the more purulent material from the nasopharynx an almost pure growth of *Streptococcus mucosus* was obtained. No bacillus influenza, *Streptococcus pyogenes* or pneumococcus was present. The acute symptoms subsided after a few days and gradual recovery ensued. No further opportunity for examination occurred. In this case we observe the appearance of the *Streptococcus mucosus* occurring simultaneously with an acute exacerbation of the symptoms and completely replacing influenza and other organisms present.

In another case chill, fever (101 F.), coryza, dryness and slight soreness of the throat, cough, hoarseness, slight nausea, soreness of muscles and joints and some headache and malaise appeared during the night. Next morning the throat appeared red; leucocytes were 13,400; cultures from the inflamed posterior wall of the pharynx showed pneumococci, few streptococci, and a strikingly large number of colonies resembling the meningococcus (about 20 per cent.); blood cultures were sterile. The next day the patient felt considerably better; the temperature was normal, and leucocytes 5,600. Two days later the patient was still indisposed and complained of dryness of the throat, hacking cough, fulness and throbbing in the head and slight fever. There were no lung findings. Examination of the sputum, which was scant and glairy, showed about 60 per cent. of the Gram negative diplococci observed previously, about 30 per cent. of the usual green colonies, and 10 per cent. of streptococcus colonies. The following day the patient was much better and continued to improve, though a hacking cough with scant expectoration continued for two weeks or more. At this time (three weeks after the onset) cultures of sputum showed many green colonies, a few streptococci, no influenza bacilli or organisms resembling the meningococcus.

A study of the meningococcus-like organism gave interesting results. It was a Gram negative diplococcus, morphologically identical with the meningococcus. It did not grow at room temperature; a luxuriant viscid

gray growth occurred on blood and ascites agar, and practically no growth appeared on plain agar. In salt solution it gave a stringy sediment commonly observed in meningococcus growths and had none of the brittle character of the growth of *M. catarrhalis*. One-third of the blood-agar slant was injected into the peritoneal cavity of guinea-pigs, which were killed in twelve to fifteen hours, and the organism was recovered from the peritoneal cavity and the heart's blood. The agglutinating power of the patient's serum for this organism was not increased above normal (1 to 10). Specific reactions with antimeningococcus sera were not made. It appears that here is an instance of an infection with an organism identical with meningococcus. There were no cases of meningitis with which the patient had recently come into contact, and this case occurred during an epidemic of grip and ordinarily would pass for a fairly typical case of influenza. No influenza bacilli occurred at any time, but the meningococcus-like organism occurred in the throat in large numbers and paralleled in a general way the clinical course. This was the only case in the series from which this organism was obtained, though organisms of the *M. catarrhalis* type were met in a variety of conditions, as will be shown later.

The findings in this case are almost identical, both clinically and bacteriologically, with those of the case of rhinitis reported by F. T. Lord[1] in 1908. Lord reviews the literature up to that time and finds only four cases, three without meningitis and one with meningitis, in which he believes the true meningococcus was isolated. Since then several investigations, especially that carried on by the New York Commission, have shown that typical meningococci are common in the nose and throat of meningitis cases and persons closely associated with them. Dunham[2] shows that there are diplococci which resemble meningococci in every way except in the agglutinating reaction. The organisms found in this case belong to the intracellularis-like organisms of his fourth group, which he states he has reason to believe are identical with the *Diplococcus intracellularis* of Weichselbaum.

Other cases are here cited to emphasize the importance in infections of this type of the *Streptococcus mucosus*. A patient was taken ill with an attack of grip. Several days later pain developed in the left ear; two days later the drum membrane ruptured and a purulent discharge continued for three days. There was severe pain in the head and the temperature ranged from 99 to 102. Three days later symptoms of meningitis appeared with high fever, delirium and rigidity of the neck, and

1. Lord, F. T.: Centralbl. f. Bakteriol., 1903, xxxiv, 641.
2. Dunham: Jour. Inf. Dis., Supplement ii, 1906, p. 10.

death occurred two days later. Spinal puncture, made two days before death, showed the spinal fluid to be under pressure. The turbid fluid obtained gave a viscid sediment on standing, many polynuclear cells and many Gram positive encapsulated diplococci, almost entirely outside the leucocytes. Cultures gave a pure growth of *Streptococcus mucosus*. This organism was highly virulent. In human blood it was nearly insusceptible to phagocytosis. Three loops of the glairy mucoid growth from the surface of blood agar suspended in 1 c.c. of salt solution, injected intraperitoneally, killed a rabbit in twenty-four hours, and one loop, similarly injected, killed an animal in thirty-six hours. The organism was recovered pure in the heart's blood and organs of the animals.

Another case gave these results: A typical attack of grip was followed in three days with otitis media and rupture of the membrane. Cultures were obtained of the sputum, from the discharge of the ear and from the nasopharynx. The ear discharge gave a nearly pure growth of *Streptococcus mucosus*. In the smears were seen Gram positive diplococci and some organisms resembled diphtheria bacilli, but which did not appear in the cultures. The sputum gave many colonies of *Streptococcus mucosus* and only a few pneumococcus and streptococcus colonies. The nasopharynx showed also colonies of *Streptococcus mucosus* and many streptococci and pneumococci. No influenza bacilli were found in any of the cultures.

Other cases of grip with complications gave a variety of results. A case with an antrum infection gave a pure pneumococcus growth from the pus, and cultures from the reddened pharynx showed about 50 per cent. pneumococci and 50 per cent. of streptococci. No *Bacillus influenza, M. catarrhalis* or *Streptococcus mucosus* was found. A frontal sinus infection following grip gave pneumococcus, 70 per cent., and streptococcus, 30 per cent. No other organisms were present. From a case of otitis media, following a severe attack of grip with slight bronchopneumonia, the ear discharge gave a pure growth of *Streptococcus pyogenes,* and the throat showed pneumococci and streptococci about equal in number to be present; no influenza bacilli.

The data given in these cases are sufficient to show that not only are influenza bacilli of minor importance in the typical cases of so-called influenza, but that they do not play an important rôle in the complications frequently associated with this condition. The bacteriologic results do not permit the implication of any one organism as responsible for the disease. On the whole, the streptococci are more numerous than in normal throats. Examination of some of the most typical cases, however, especially early in the attack, shows almost pure pneumococci on the

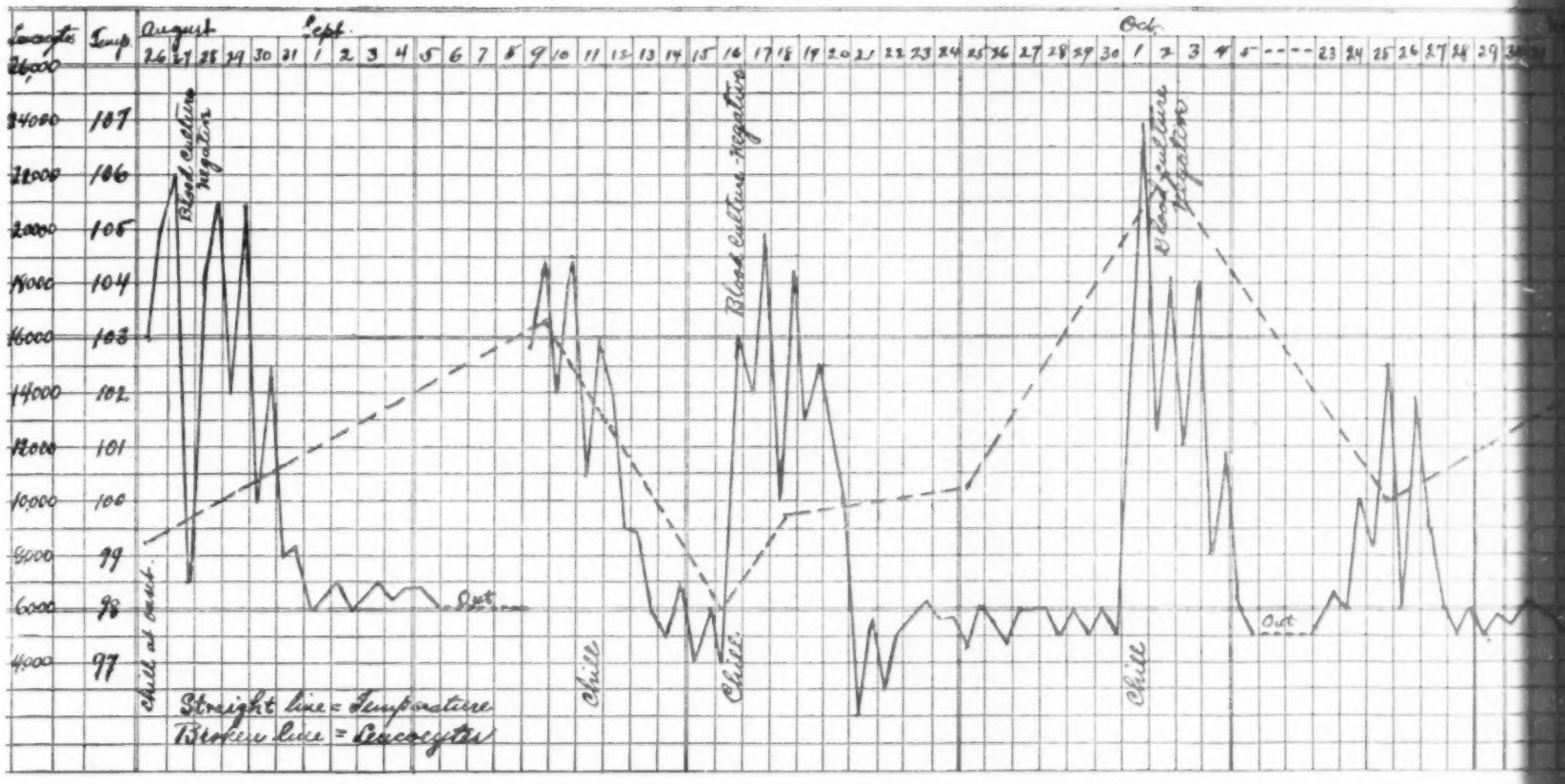
inflamed surfaces in the throat. It is certainly true that pneumococci are the most common organism present early in the disease, before time has elapsed for the invasion of other pathogenic bacteria, which seems nearly always to occur.

The *Streptococcus mucosus* is an extremely interesting and important organism. It is not uncommonly found in various conditions associated with lesions in the respiratory tract. I have found it in the sputum in acute articular rheumatism, lobar pneumonia, grip, otitis media, and cerebrospinal meningitis. It is an organism that seems especially prone to invade the Eustachian tube, produce otitis media and involve the meninges. Schottmüller, who was among the first to call attention to this organism, observed it in seven cases, three of which were meningitis following otitis media. Several other writers have described it in a variety of throat and other affections.

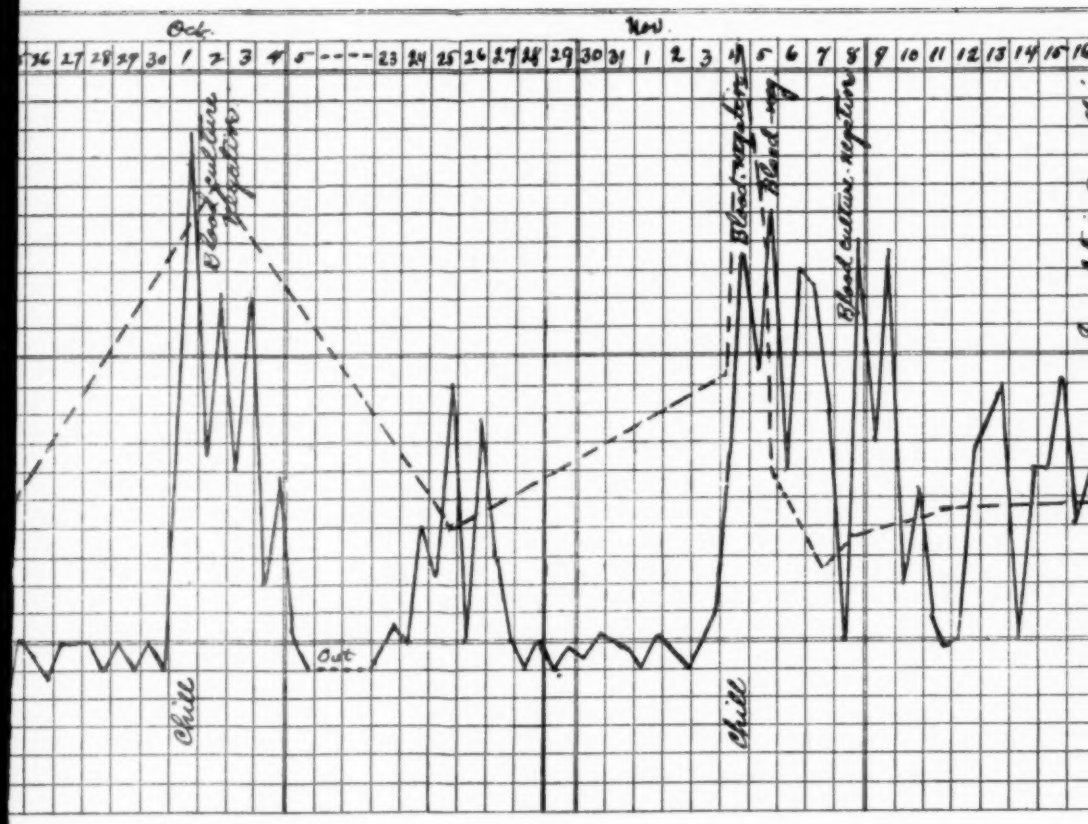
The *M. catarrhalis* is common in both normal and diseased throats. Little doubt exists but that there is a large group of organisms of this type varying considerably in their properties and in their pathogenicity. As a rule, organisms of this group may be readily differentiated from meningococci by their cultural reactions. Some, however, resemble the latter organism more closely, as has been shown by Dunham.[2]

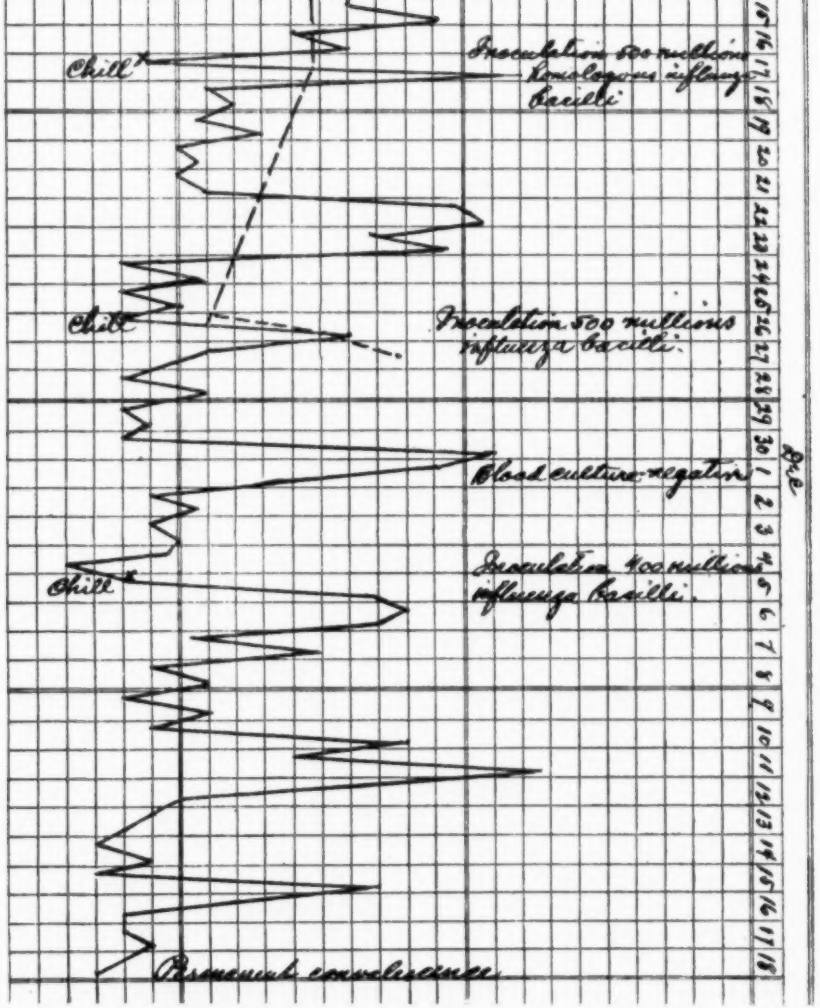
The question may now be asked, What the etiology is of this clinical condition known as influenza or grip? There can be little doubt but that the pandemic of 1889-90 was caused by Pfeiffer's bacillus. The bacilli, as was shown by Pfeiffer and confirmed by numerous other observers, occurred at the inflammatory site in enormous numbers in pure culture. They were present early in the disease and in a general way paralleled the clinical course. Animal experiments were suggestive, though not conclusive. They have been found in other epidemics of the disease in practically all parts of the world. But, granting this, the important fact remains that typical epidemics occur, clinically identical with those referred to, in which, however, no influenza bacilli can be found in the respiratory secretions or other parts of the body. This has been found by numerous observers, among whom may be mentioned Rosenthal, Sacquépée, Besançon and Israel de Jong, Kleinenberger, Lord, von Jaksch and Jochmann. The bacilli of *M. catarrhalis* and diphtheria-like bacilli, usually in mixed culture, are the most common bacteria found in these conditions.

The tendency is natural in studying an epidemic to assume that there is but one causative organism. If this is true, in epidemics of grip the causative organism is unknown. The facts in this paper, however, and the trend of investigation appear to show that the same clinical condi-



ARCHIVES OF INTERNAL MEDICINE—ILLUSTRATING ARTICLE BY DAVID J. DAVIS, M.D.


Oct.
Nov.
26 27 28 29 30 1 2 3 4 5 --- 23 24 25 26 27 28 29 30 31 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Blood culture negative
Blood culture negative
Blood culture negative
Chill
Out
Chill


Chill
Inoculation 500 millions Pneumococcus influenza Bacilli
Chill
Inoculation 500 millions influenza Bacilli.
Blood culture negative
Chill
Inoculation 400 millions influenza Bacilli.
Permanent convalescence
Dec

tion may be produced by a variety of organisms. The underlying factor which stimulates or permits these organisms to develop must be sought in climatic or other conditions. The various organisms occurring in this condition are practically always found in small numbers in normal throats. Some injury to the upper respiratory tract, for instance, abnormal circulatory disturbances, offers the conditions favorable for the development of these bacteria, and particularly for an increase in virulence. This is exactly analogous to the increase in virulence of intestinal bacteria after an injury to the intestine, for instance, acute intestinal obstruction, as has been demonstrated experimentally. The increase in virulence having been established, the bacteria carried from person to person readily produce the same clinical conditions, being aided perhaps by the same factors on the part of the host that originally developed the virulence in the bacteria.

STUDIES OF INFLUENZAL PNEUMONIA.

During the past year a considerable number of cases of an acute pneumonic infection have entered the Presbyterian Hospital. The disease has occurred largely among foreigners, particularly Greeks. By many physicians it is called grip pneumonia; others call it acute pneumonia, bronchopneumonia or lobular pneumonia. The clinical course in these cases is very similar and suggests a common cause.

Observations were made on a series of forty-two cases. The onset, as a rule, is sudden, beginning, as the patients usually state, with a cold. They have chills, a slight cough, expectoration, scant at first and becoming more profuse, some malaise, headache, pains in back and legs, and usually, a day or two later, diffuse or localized pain in the chest, which is made worse by coughing and deep breathing. Occasionally they complain of slight soreness of throat, but, as a rule, this symptom is not marked. Prostration, while marked in some cases, can not be said to be a characteristic feature. The temperature promptly rises; in severe cases it reaches 106 and higher. As a rule, it rises to 101 or 103, fluctuates for a time and reaches normal in a few days by a gradual fall. At times it descends so quickly that it closely resembles a crisis; again it may become intermittent or remittent in type for a few days and gradually fall to normal.

Physical examination, as a rule, shows areas of harsh breathing, with here and there coarse moist râles. Crepitant râles usually are not present. Dulness on percussion is slight, often not perceptible, and rarely is bronchial breathing heard. Vocal and tactile fremitus is usually normal and there is no tendency for the involved areas to be limited to lobes.

In some cases the process is diffuse and apparently involves the larger tubes only.

Recurrences are not uncommon. Six of the forty-two cases each had one or more relapses, occurring usually within two or three weeks after the first attack. Generally the patient was up and about for a few days, not having entirely recovered, when suddenly he would be taken with a chill and fever and a return of the symptoms. In one rather remarkable case there were at least seven distinct recurrences of chills, fever, rise in leucocytes, etc., with final recovery (Chart 1). The cases were remarkably free from complications. The urine, as a rule, was normal; occasionally there was a small amount of albumin and a few granular casts.

A leucocytosis occurred in nearly every case. In the milder cases the leucocytes usually varied from 10,000 to 15,000. In the severer cases they numbered from 20,000 to 25,000 or higher. The increase was chiefly in the polynuclear cells.

Blood cultures were made in the series with few exceptions and the results were uniformly negative. Various media were used, including broth, ascites broth, milk, pigeon-blood broth, and media containing other bacteria. This latter method was used with the idea of obtaining growth of influenza bacilli because of their symbiotic relationship to other bacteria. Inoculations were made at various times during the course of the disease, always when the patient had elevation of temperature. Large, moderate and small quantities of blood, drawn from the arm, were introduced into the media.

The sputum in these cases at first was scant, later becoming more profuse and purulent. Rarely it contained traces of blood as fine streaks, and not intimately mixed, as in rusty sputum. In twenty-six cases it was washed and plated in the usual manner on blood-agar plates, pigeon-blood being used in most cases. Influenza bacilli were isolated ten times. In most cases in which they were found at all they were the predominating organism in the sputum. Cultures made at different times during the course of the disease gave results pointing to a varying bacterial flora. In the early stages the influenza bacilli, as a rule, were not found, pneumococci and streptococci being abundant on the plates. Then suddenly influenza bacilli might appear in the cultures without any corresponding change in the clinical condition. The *Micrococcus catarrhalis* was found only occasionally, and in no instance was it the predominating organism.

The accompanying chart is intended to summarize some of the findings in a remarkable case of the recurrent type. The patient finally recovered completely. There were at least seven distinct chills, followed

by a prompt rise in temperature. Blood cultures were made at seven different times, before, during and after chills, always with negative results. The leucocyte curve was variable, at times during the height of the fever rising above 20,000. Cultures of the sputum were made at intervals during the course of the disease, and in every instance the influenza bacillus was present in almost pure culture, appearing in clusters about the few streptococcus and pneumococcus colonies on the plates. During the recurrences, as shown in the chart by the elevation of temperature, no change occurred in the bacterial flora in the sputum.[3]

The serum in this case, tested at three different times during the course of the disease for specific agglutinins, using the homologous influenza bacillus, failed to react in each instance. Both the microscopic and macroscopic methods were used. In both normal and patients' sera slight agglutination usually occurred at a dilution of 1 to 20. Six other cases were tested for specific agglutinins, using homologous influenza bacilli. All gave negative results, except that in one instance there appeared some clumping at 1 to 50 dilution in the patient's serum, and 1 to 20 in the normal. Evidently in these cases, though the sputum may be teeming with influenza bacilli, the agglutinins are either not produced at all or only to a slight extent.

Opsonic determinations were attempted in a number of cases, but abandoned as unreliable because of the difficulty in obtaining a proper suspension and on account of spontaneous phagocytosis.

Most of these cases clear up so rapidly under the rest treatment that the inoculation treatment is evidently inapplicable. In the recurrent cases of a more subacute or chronic character with large numbers of influenza bacilli in the sputum, injections of dead organism should be tried. In the case referred to above three injections, each of approximately 500 million homologous influenza bacilli, were given. A chill, followed immediately by a rise in temperature of short duration and considerable local reaction, occurred after each injection (Chart 1). Injections were made in other cases of similar amounts, resulting in a local reaction, but there was not the chill and rise in temperature observed in this case. They gradually recovered, as they usually do, without injections. No conclusions should be drawn.

DISTRIBUTION OF INFLUENZA BACILLI.

How commonly the influenza bacillus occurred in various infections in the respiratory tract and other parts of the body before the epidemic of 1889-90, at which time the organism was discovered, we shall never

3. The blood was repeatedly examined for malaria parasites with negative results. The result of the tuberculin test was also negative.

know. For a time after its discovery the idea prevailed that it was found only in influenza, though Pfeiffer, in one of his first papers, described organisms of this type found in other diseases which he called pseudo-influenza bacilli. Since that time it has been shown that bacilli indistinguishable from influenza bacilli occur in diseases other than influenza, and that Pfeiffer's pseudo-influenza bacilli can not be distinguished from bacilli from influenza cases. The statement appears not infrequently in the literature that the epidemic of influenza in 1889-90 spread the infection throughout the world, and since that time the bacilli, being almost ubiquitous, play an important rôle as secondary invaders in many diseases, especially tuberculosis. This is also given as an explanation for the frequent outbreaks of influenza epidemics since that time. Many of these, of course, are not epidemics of influenza infections. That influenza bacilli were as common before 1889 as since is probable, since epidemics of influenza have spread over the earth many times in the past, and the bacilli would have remained to produce secondary infections after these, as they did after the last pandemic.

The influenza bacillus is an extremely common organism in the respiratory tract in various infections. Occasionally it is found in the body in other localities. Thus there are cases described of cholecystitis, arthritis, pyelitis, cystitis, otitis media, empyema, etc., caused by bacilli of this type.

The accompanying table is arranged to show the occurrence of influenza bacilli in the throat or sputum in a variety of diseases which more or less affect the respiratory tract:

TABLE SHOWING THE OCCURRENCE OF INFLENZA BACILLI IN VARIOUS DISEASES.

Disease.	Total No. Cases.	B. influenzæ Present.	B. influenzæ not Found.	Postive findings, Per Cent
Pertussis	68	61	7	89
Varicella	11	7	4	64
Measles	23	13	10	56
Lobar pneumonia	12	4	8	33
Acute articular rheumatism	11	0	11	0
Bronchopneumonia	26	10	16	38
Pulmonary tuberculosis	5	3	2	60
Ep. Cerebrosp. meningitis	11	4	7	30
Influenza (1905)	17	3	14	17
Influenza (1908)	23	4	19	18
Normal	20	2	18	10
Total	239	116	123	48

In pertussis they are present in nearly every case, sometimes during the course of the disease, usually after the paroxysmal stage sets in. They

may remain in the throat for a considerable period of time after the spasms disappear. In some cases the bacilli are very numerous, and on the plates are in almost pure culture, while in other cases they are few. In some cases they may be persistently absent and suddenly appear in enormous numbers and thus continue. Pneumococci and streptococci are nearly always found and not infrequently bacilli of *M. catarrhalis* and diphtheria-like organisms appear in culture in small numbers.

In measles they are common, especially in the cases in which cough is a pronounced feature. *M. catarrhalis* was commonly found also. Varicella gave much the same bacteriologic findings as measles.

In lobar pneumonia usually the pneumococcus is the predominating organism in the sputum. Streptococci are present in small numbers. Influenza bacilli were present in the sputum four times in twelve cases examined. In one case it was interesting to note that even early in the disease (fourth day) these bacilli were present in the typical pneumonic rusty sputum in numbers far exceeding pneumococci. In another case of a somewhat typical pneumonia in which, however, pneumococci were obtained in the blood in pure growth, examination of the washed sputum on the fourth day of the disease gave 80 per cent. *M. catarrhalis* colonies and 20 per cent. pneumococcus colonies. No influenza bacilli were present. Subsequent examinations gave similar findings. An elderly man became ill with symptoms of lobar pneumonia. The sputum at first was bloody and later became profuse and purulent. The clinical diagnosis of abscess of the lung was made. Examination of the washed sputum gave enormous numbers of influenza colonies, chiefly in clusters about colonies of other bacteria. Of the remaining colonies, 75 per cent. were typical *Streptococcus pyogenes* and 25 per cent. were *Staphylococcus pyogenes aureus*. No pneumococci appeared in the plates. A few days later death occurred. Postmortem examination showed lobar pneumonia with several abscesses in the lungs. Pus from an abscess gave pneumococci 60 per cent., streptococci 35 per cent., and *Staphylococcus aureus* 5 per cent. No influenza bacilli were found. These cases are instructive in showing the variation in the bacterial flora, not only in complicated cases such as the last, but even in typical cases of pneumonia.

The results obtained in acute articular rheumatism are interesting in that they show more than in any other condition except tonsillitis a predominance of streptococcus colonies. The bacterial flora of the throat in these two conditions is about the same. Influenza bacilli were not found in any of the cases examined. In one case the *Streptococcus*

mucosus was obtained in large numbers in the sputum and nasal secretions.

Only five cases of pulmonary tuberculosis were examined. Influenza bacilli were found in three of these. It has been observed by many that they are common, secondary invaders in this disease. In epidemic meningitis they were found in the nose and throat four times in eleven cases.

In normal throats they are occasionally found. Swabs of the throat from twenty normal persons gave growth of influenza bacilli twice; they were present in small numbers.

Of 239 cases examined with special reference to influenza bacilli, 116, or nearly 50 per cent., showed the presence of this organism. The table shows them to occur fairly uniformly in the various diseases. It may be stated as generally true that they are found more frequently and in larger numbers in those cases in which there is involvement of the bronchi, especially chronic cases with profuse expectoration, than in conditions like tonsillitis and acute rheumatism, in which the lesions are limited to the upper respiratory tract.

What is the significance of this common distribution of these organisms? In order to answer this question the pathogenic properties should be inquired into. For animals they are not highly virulent. One or two slant agar growths injected into the peritoneal cavity of a guinea-pig or small rabbit will cause death in twenty-four hours and the bacilli will be found in the heart, blood and organs of the body. Injected into the human throat (organism from pertussis) it produces pharyngitis, cough, profuse glairy expectoration, fever etc., and the bacilli grow luxuriantly for weeks under these conditions.[4] Injected in living culture (organism from bronchopneumonia) subcutaneously in the human being they produce local swelling, redness and tenderness, and after several days an abscess containing yellow pus in which the bacilli thrive and from which they may be recovered in pure culture.

The above facts indicate that these organisms are at least not always harmless saprophytes. It is undoubtedly true that they play no rôle whatever in many of the infections mentioned. While making cultures at frequent intervals during the course of the infection I have several times noted the sudden appearance of influenza bacilli in large numbers with no change in the clinical course. On the other hand, taking into consideration all the data in the table, it is generally true that the influ-

4. Bacteriology of Whooping Cough, Jour. Infect. Dis., 1906, iii, 1.

enza bacilli were more commonly found in the severer cases, and especially in those cases in which bronchial complications existed. The deaths in the series were too few to permit one to draw conclusions on this point, there being only nine in 230 cases in which the termination was known.

In this connection may be mentioned the possible significance of symbiosis in influenza infections. In the presence of other bacteria the influenza bacillus grows much more luxuriantly than when alone. It has also been demonstrated by animal experiments[5] that a few bacteria, harmless in themselves, introduced into an animal with influenza bacilli, greatly increase the virulence of the latter. Experiments indicate little differences among the bacteria to accelerate the growth of influenza bacilli. It may very well be, however, that their biologic properties may be profoundly changed by the presence of certain other bacteria, and consequently the variety and virulence of associated bacteria may be important in determining the virulence of the influenza bacillus. The presence of various bacteria in infections with the occurrence of hemoglobin in the inflammatory secretions may have something to do with the appearance, at times late in the disease, of such enormous numbers of influenza bacilli in the sputum.

CONCLUSIONS.

1. In many epidemics of clinical influenza or grip the influenza bacillus plays little or no part as an etiologic organism.

2. These epidemics appear to be due to a variety of organisms—the *Pneumococcus, Streptococcus pyogenes, Streptococcus mucosus* and *Micrococcus catarrhalis* being most commonly found in the secretions. An organism morphologically and culturally identical with meningococcus was found in one case.

3. Complications following these cases are often serious and usually due to *Pneumococcus, Streptococcus pyogenes* and *Streptococcus mucosus.*

4. The influenza bacillus is often found in so-called influenzal pneumonia, but not in all cases. It can not be considered the primary cause. An abundant mixed bacterial flora is characteristic of the respiratory secretions in these cases.

5. Influenza bacilli are commonly found in a great variety of infections (Table 1).

5. Jacobson: Arch. de méd. expér., 1901, xiii, 425. Davis: Jour. Infect. Dis., 1906, iii, 22.

6. Experiments both on animals and human beings demonstrate that these bacilli possess pathogenic properties. They are often, or at least sometimes, non-virulent as they occur in the secretions.

7. As secondary invaders they undoubtedly unfavorably influence other primary infections.

NOTE.—This work was done in the Pathological Laboratory of Rush Medical College, through the aid of the Alumnæ Fellowship Fund, and under the direction of Dr. Hektoen. Much of the material was obtained at the Presbyterian Hospital, from the service of Dr. Billings, to whom I am greatly indebted. The remainder came from other services of the Presbyterian Hospital, from Cook County Hospital and from outside sources. I desire to express my thanks to the numerous physicians and to the physicians of these hospitals for their help in obtaining material and for their many courtesies.

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HEART-BLOCK IN THE VENTRICULAR WALLS.

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Physiologic and clinical studies have emphasized the fact that the two ventricles of the heart ordinarily act as a unit, all parts contracting approximately at one time and with all the force of which they are capable at that moment. Under exceptional circumstances, however, the ventricular contractions may be more or less abnormal, because there is some incoordination either between the two ventricles or between different portions of the ventricular musculature.

The following case illustrates several abnormal forms of ventricular contraction which are interesting because they were observed clinically and because some of them, at least, resulted from the action of strophanthin on an irregularly acting heart. The abnormalities will be discussed in the following order: 1, ventricular contractions which produce waves in the jugular pulse, but little or no effect on the apex tracing; 2, the superposition of one systole or partial systole on another; 3, a delay in the onset of systole of the right ventricle.

The patient on whom these observations were made came to the medical dispensary of the Cooper Medical College, March 26, 1908, complaining of shortness of breath and a lump in the stomach. He was a teamster and had always worked hard and drunk heavily. He had had gonorrhea but denied syphilis. About five months before, while doing some heavy lifting, he first noticed his shortness of breath. This had gradually grown worse, more particularly in the past few days, and on this account he had been unable to sleep for several nights. His urine had diminished in amount and his feet and abdomen had become swollen. In addition to these symptoms, he had suffered for several months from what proved subsequently to be a rather tender epigastric hernia of moderate size.

On examination he presented the appearance of a large, powerful man in the extreme stages of cardiac decompensation. His cyanosis and dyspnea were extreme. His heart was markedly enlarged, the point of maximum impulse being plainly felt in the fifth intercostal space 12 cm. to the left of the midline, and the right border being 6 cm. to the right. Auscultation showed only a rapid heart action with embryocardia and a slight systolic murmur at the apex. The pulse was small, regular and rapid, 140 to 160 to the minute. The cervical veins were distended and markedly pulsating. The liver could be felt 5 cm. below the costal mar-

gin, rather tender and distinctly pulsating. Considerable fluid was present both in the abdomen and in the two pleural cavities. There was moderate edema of the genitals and legs. The urine was highly colored, but free from albumin. Venous tracings (Fig. 1) taken at this time showed a positive venous pulse and an absence of auricular waves.

On account of the patient's serious condition, he was sent into the

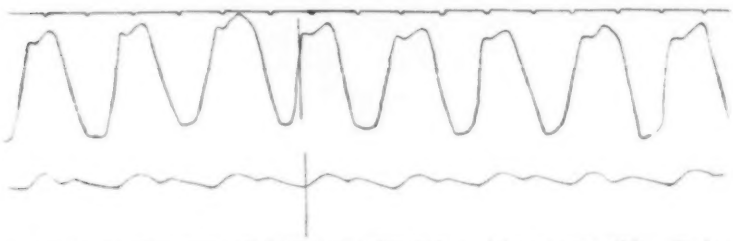

Fig. 1.—Jugular and radial tracings taken before giving strophanthin. Tachycardia with a positive venous pulse. Time, 1/5 second.

Lane Hospital and was immediately given an intravenous injection of one milligram of strophanthin. Within a few minutes his pulse changed most remarkably. It began to intermit, but at the same time it became stronger. After an hour it had fallen to about 70 a minute and was of fair size but very irregular. Coincident with this change in the pulse, the patient showed a very marked improvement in his general symptoms. He became less dyspneic, less cyanotic, and much less distressed generally. Venous and liver tracings still showed the positive venous pulse

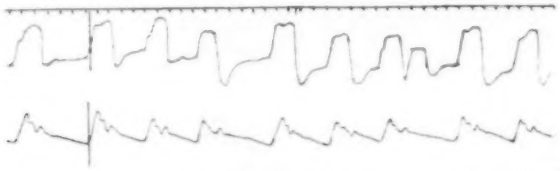

Fig. 2.—Jugular and radial tracings one-half hour after strophanthin injection. Time, 1/5 second.

with absence of the a-wave. It was now the typical irregular pulse of auricular paralysis (Fig. 2). The patient gradually improved during his stay in the hospital; so much so that before leaving his ventral hernia was operated on and cured.

During his whole stay, however, his venous and liver pulses remained of a positive type, for the most part quite irregular and without evidence

of auricular contraction. The slight systolic murmur heard at the apex on admission disappeared. Neither second sound was accentuated. It is difficult to say whether the positive venous and liver pulses were due in his case to an auricular paralysis alone or whether there was in addition a tricuspid regurgitation without murmurs. I am somewhat inclined to the latter view on account of the marked liver pulse and the tendency to plateau on the venous tracings.

During his stay in the hospital the patient presented periods of regular heart action associated with a positive venous pulse. In order to study the relation of this regular heart action to the irregular, a great number of venous tracings were taken. These failed to demonstrate any definite evidence of auricular contractions even during the regular heart action. Among them, however, several distinct abnormalities in the character of the ventricular contractions were encountered.

The first of these was the occurrence of ventricular contractions which produced waves on the jugular pulse, but had little or no effect on the apex tracing. Ordinarily in auricular paralysis a ventricular contraction manifests itself graphically by an arterial pulse, by waves on the cardiogram and by marked positive waves during systole on the venous and liver pulses. Sometimes no arterial pulse is produced because the systole is of insufficient force to open the aortic valves and to send blood into the arteries. The apex tracing, therefore, gives us more reliable evidence of ventricular contraction than does the arterial pulse.

In certain venous tracings from this patient, however, a series of waves were encountered between or just before the definite systoles (Figs. 3, 4, 5, 6). These were not the single waves of mid-diastole which follow the preceding systole by a definite interval and which are frequently met in tracings from patients with auricular paralysis. Such waves are probably identical with the wave described by Hirschfelder and others.[1]

The waves seen in this patient were far too numerous and too variable to be explained as h-waves. For them two possible causes must be considered. In the first place such waves might be produced by irregular auricular contractions which were not followed by ventricular systoles. In such a case they would be comparable to blocked auricular extrasystoles[2] or possibly to some form of auricular fibrillation. This patient,

1. Hirschfelder, A. D.: Some Variations in the Form of the Venous Pulse. Johns Hopkins Hosp. Bull., 1907, xviii, 265. Gibson, A. G.: The Significance of a Hitherto Undescribed Wave in the Jugular Pulse, Lancet, Nov. 16, 1907.

2. Wenckebach, K. F.: Beiträge zur Kenntnis der menschlichen Herztätigkeit (part 2), Arch. f. Anat. u. Physiol (physiologic section), 1907, p. 1. Hewlett, A. W.: The Blocking of Auricular Extrasystoles, Jour. Am. Med. Assn., 1907, xlviii, 1597.

however, gave no definite evidence at any time of auricular contractions either in the jugular or liver pulses or in the apex tracing. At the time when these waves were observed his pulse presented all the signs of the absolutely irregular rhythm of auricular paralysis. It would seem rather improbable, therefore, that these venous waves should be due to auricular contractions.

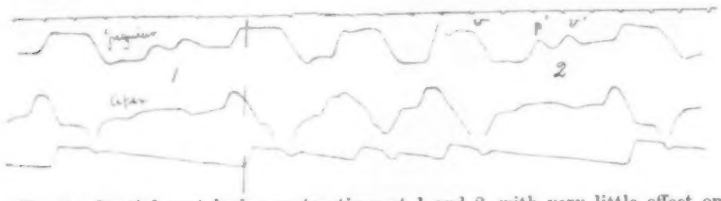

Fig. 3.—Partial ventricular contractions at 1 and 2, with very little effect on apex. Figure reduced one-half.

Another possible explanation for these waves is that they were due to weak or partial ventricular contractions. It appears at first thought rather improbable that ventricular contractions should affect the venous pulse, but not the apex tracings. However, a careful study of certain transition forms seems to confirm this view. In the first place, the venous waves frequently occurred in pairs, p′ and v′, just as do the waves in the ordinary ventricular contractions (Fig. 3). In the second place, where the waves were well marked the systole was often indicated on the

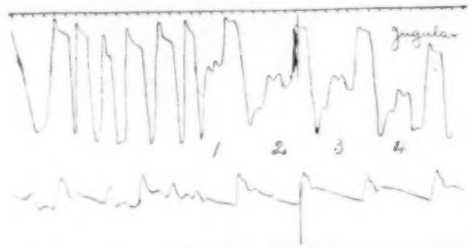

Fig. 4.—Transition of fairly well-marked positive venous pulse 4 to a series of ill-defined waves at 1. At 1 the abnormal ventricular contraction is immediately followed in a normal forceful contraction without an intervening diastole.

apex tracing. In Figure 3, for example, it will be seen that each pair of venous waves is accompanied by a slight but definite elevation in the apex tracing. Were these venous and apical waves due to auricular contractions, one would expect to find two separate elevations on the apex tracing corresponding to those on the venous pulse instead of the apex plateau, which denotes a single rather prolonged contraction.

Finally some of these extra venous waves bear a close resemblance to the ordinary venous waves, there being a definite transition between the two. This is well illustrated in Figure 4. In this tracing a number of jugular pulses are seen which are not accompanied by radial pulses. Those marked 2, 3 and 4 resemble the ordinary positive pulses; yet these show definite transitions to the series of ill-defined waves marked 1.

It seems to me quite certain that we are dealing here with slight or partial ventricular contractions which either do not affect the apex tracing at all or else do so to a very slight extent.

If this conclusion be correct, then Figure 4 becomes interesting from another standpoint, because it shows how a systole may be superimposed on one of these partial systoles without any intervening diastole. The partial contraction in 1, for example, had hardly reached its height before a second and effectual systole took place. The same is illustrated in Figure 5 at 1 and 2.

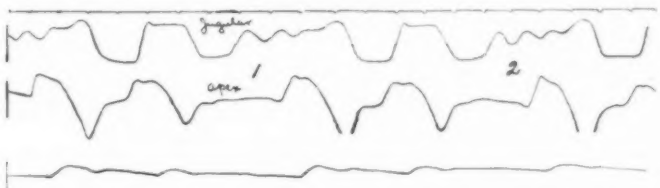

Fig. 5.—Partial ventricular contraction at 1 and 2, immediately followed by a normal forceful one without an intervening diastole. Figure reduced one-half.

Mackenzie has noted somewhat similar waves to those here described on the venous pulse of absolutely irregular hearts. In one case where they evidently corresponded to ventricular contractions[3] he ascribes them to contractions of the right ventricle independent of the left. In other places where the relation to ventricular systoles was less definite, he is inclined to attribute them to auricular fibrillation.[4] Schmoll[5] interprets somewhat similar waves as due to partial ventricular contractions. He proposes the term "ataxia of the heart" to cover such instances of incoordinated contractions. Aside from these, I am unable to find any ref-

3. MacKenzie, James: The Study of the Pulse, p. 294, Fig. 310.

4. MacKenzie, James: The Interpretation of the Pulsations in the Jugular Veins, Am. Jour. Med. Sc., 1907, cxxxiv,-12, Fig. 24. Abnormal Inception of the Cardiac Rhythm, Quart. Jour. Med., 1907, i, 39, Fig. 10.

5. Schmoll, E.: Ataxia of the Heart, read before the California Academy of Medicine, May, 1908.

erences in literature to waves on the venous tracing from cases of auricular paralysis which resemble those just described in this case.

The third abnormality in the ventricular contractions is illustrated in Figure 6. A study of this figure shows that the venous waves 1, 2 and 5 are of the type commonly met in auricular paralysis. They begin just after the apex beat and just before the radial pulse and consist of two ill-defined waves, p and v, united by a distinct plateau. In the contraction marked 3, however, the venous pulse does not begin until after the radial pulse. In other words, the force that produces the p-wave does not begin to operate until some little time after the left ventricle has passed into contraction. I believe that the p-wave is sent back into the vein through the motionless auricle by the onset of contraction of the right ventricle.[6]

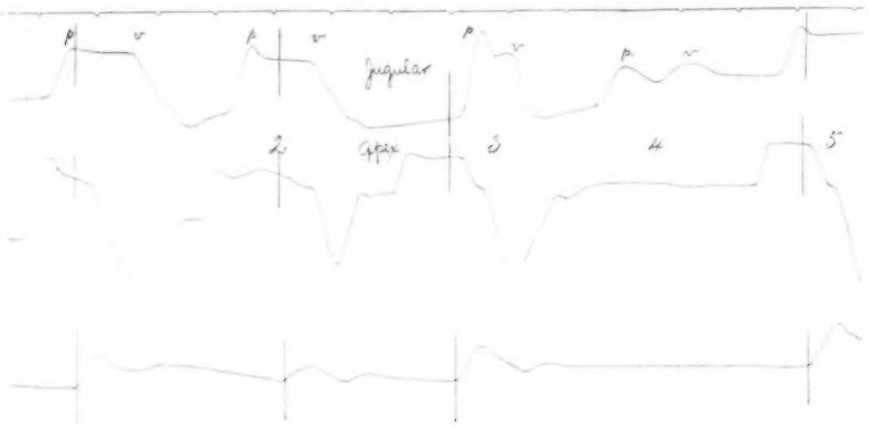

Fig. 6.—Contractions 1, 2 and 5 are of the type ordinarily met in auricular paralysis. Contraction 4 produces waves on venous pulse, but little effect on apex. Contraction 3 shows marked delay in onset of venous wave. Wave terminates as usual.

The late appearance of the p-wave, therefore, would indicate that the right ventricle has contracted some little time after the left. A dozen or more similar delays in the systole of the right ventricle could be picked out from my tracings, but they do not differ materially from that shown in this figure. It is interesting to note that, even though the systole of the right ventricle begins late, the diastole occurs at the normal time.

6. Hewlett, A. W.: The Interpretation of the Positive Venous Pulse, Jour. Med. Research, 1907, xvii, 119.

This will be seen by comparing the jugular and apex tracings in the normal and abnormal contractions of Figure 6.

These various abnormalities in the ventricular contractions bore a definite relation to the administration of strophanthin to this patient. The delayed contractions of the right ventricle occurred only after this drug had been given and were noted on two of three occasions a few hours after the intravenous injection of one milligram. The ventricular contractions which produced waves on the venous pulse and not on the apex tracings were found once or twice when the patient had not been taking strophanthin. After taking one milligram of this drug, however, they occurred regularly within a few hours.

The nature of these various abnormal ventricular contractions is not altogether clear. The delayed systole of the right ventricle is, perhaps, the easiest to explain. This was a delayed but not a weak contraction. In other words, it must be assumed that the ventricular muscle was capable of performing an active contraction, but that the stimulus reached it abnormally late. There was then some sort of a block to the stimulus destined for the right ventricle. Whether or not this block occurred in the right limb of the His bundle can not be definitely answered, but the hypothesis is an attractive one.

The other abnormalities in ventricular contraction are more difficult to explain. They are slight or partial contractions, in many instances immediately succeeded by normal contractions. It seems rather improbable that these small contractions should represent weak systoles involving the whole heart. According to the law of all or nothing, the heart muscle responds to a stimulus with all the force of which it is at the time possessed. Had the entire ventricular muscle obeyed this law it is difficult to see why these slight contractions, hardly begun, should be followed by normal forceful contractions. It seems to me much more likely that the small waves were produced by contractions of a portion only of the ventricular musculature. In such case the remaining unused muscle would be ready to respond to an immediately succeeding stimulus with a normal forceful contraction.

This view is supported by the fact that these abnormal contractions were greatly favored by the use of strophanthin. It is well known that strophanthin, in common with other members of the digitalis group, tends to inhibit the passage of stimuli from one portion of the heart to another. The fact, then, that these abnormal systoles were favored by strophanthin gives support to our belief that they were partial ventricular contractions due to a blocking of the stimulus and a limitation of its effect to one part of the muscle. This view is also supported by the

simultaneous occurrence of delayed contractions of the right ventricle which were almost certainly due to some sort of blocking.

The possibilities of partial contractions of ventricular musculature or of blocks within the ventricles do not seem to have been generally considered. The latter has been offered by Schmoll[7] as an explanation for the slow heart action which occurs during the paroxysms of Adams-Stokes' disease in complete heart block. The occurrence of partial contractions has been observed experimentally in dying hearts, one ventricle stopping before the other. It has also been observed before the ventricles pass into fibrillation, at which time they often show waves of contraction involving only a part of the muscle. Clinicians have approached this subject in the discussion of hemisystole. According to von Leyden,[8] it is possible for the right ventricle to beat independently of the left. von Leyden's tracings, however, admit of an entirely different interpretation,[9] so that the hypothesis of hemisystole has rather fallen into disfavor. Nevertheless, Mackenzie has noted at least one instance of the condition in a dying heart.[10] More recently Kraus and Nicolai[11] have advocated the possibility of hemisystole, basing their conclusions both on experiment and on evidence derived from electrocardiograms. Schmoll[5] has also called attention to the possibility of partial contractions of the ventricles and proposed the general name of ataxia of the heart for such conditions. One may well speak of ataxic contractions of the ventricles in the case that I have just described, for the systoles were incoordinated, and for this reason more or less ineffectual. The relation of such contractions to fibrillation of the ventricles should not be overlooked. Before the ventricles pass into fibrillation they frequently show incoordinated waves of contraction, involving only a part of the musculature. On account of this relation to fibrillation and on account of the ineffectual character of many of the contractions in my patient, it was deemed unsafe to continue the strophanthin injections beyond the three that he received. One danger of such injections consists in the fact that there are no means of controlling the action of the drug after it has once been given.

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7. Schmoll, E.: Deutsch. Arch. f. klin. Med., 1906, lxxxvii, 554.

8. Recently reviewed by von Leyden and Bassenge: Ueber ungleichzeitige Kontraktion der beiden Herzventrikel (Hemisystole), Ztschr. f. klin. Med., lxiv, 1.

9. Hering, H. E.: Deutsch. med. Wchnschr., 1903, No. 22, p. 381.

10. MacKenzie, James: The Study of the Pulse, p. 296, Fig. 314.

11. Kraus and Nicolai: Ueber die functionelle Solidarität der beiden Herzhälfte, Deutsch. med. Wchnschr., 1908, xxxiv, 11.

CONCLUSIONS.

1. Ventricular contractions may cause waves on the jugular pulse with little or no effect on the apex beat.

2. Such contractions may be followed immediately by normal contractions without a diastolic period.

3. The right ventricle may begin its contraction distinctly later than the left.

4. In my case these were largely strophanthin effects.

5. They are probably to be interpreted as instances of intraventricular heart-block.

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THE RÔLE OF FERMENT-REVERSIONS IN METABOLISM.*

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The biologic sciences are rarely able to avail themselves of the use of theory, as can so commonly be done in the physical sciences, in such a way that the theory serves as a prophecy for the future, as well as an articulation with the past. When, however, phases of biologic knowledge are securely founded on a physical basis, it becomes possible to review a subject from the point of view of theoretic interpretation. Within recent years such a procedure has become possible in several directions in physiology.

The subject of the rôle of ferment-reversions in metabolism is naturally one of great interest; and, as the barristers say of a line of interrogation in the introduction of evidence, the proper foundation has been laid for it. It must be clearly realized, however, that if such a procedure as I contemplate is to be made profitable, the scope of inquiry must be extended to the broadest limits of biologic matters. The inquiry may be made under three general headings:

1. What is the status of the theory of reversion of chemical and physical reactions in the pure sciences?
2. What are the specific facts tending to demonstrate that the theory holds in the concrete sense in biologic material?
3. What are the facts in physiology, as yet more or less devoid of reasonable explanation, that may be logically classed as instances of such reversions, and grouped as such under a comprehensive theoretic interpretation?

Finally, it will be interesting to contrast the physiologic with the physical station of equilibrium.

The types of reaction concerned in the reversion within biologic bodies are varied. Many of them are anhydrations, condensations, reactions in which water is added to form larger molecules; such are the reactions concerned in the synthesis of carbohydrates, fats and proteins. Others are reductions and oxidations. Very important from the constructive point of view are the intramolecular rearrangements. Of this class there are two groups, depending on whether the mass of the molecules is invariable or varied. An illustration of intramolecular rear-

*Lecture delivered before the Harvey Society, April 18, 1908.

rangement without alteration in molecular mass, strictly isomeric, is to be noted in the sugars. Within the body the three hexoses, d-glucose, d-galactose and d-levulose, are subject to conversion into one another. That the different hexoses tend thus to pass into the isomeric sugars as a chemical reaction was shown years ago by Lobry de Bruyn and Van Ekenstein. These reactions, as will be pointed out, are of very widespread occurrence in the vegetable kingdom. Illustrations of intramolecular rearrangements, which are of the greatest importance, including alterations in the molecular mass, are to be found in the different forms of protein reactions.

The term "ferment-reversions" constitutes a verbal incongruity. The reactions under consideration are, of course, not inaugurated by the presence or the action of the ferments; the enzymes simply accelerate the velocity of already progressing reactions. The autoreactions that are accelerated by enzymes are, in themselves, the expressions of the reaction-qualities of the substance involved and progress to an equilibrium in accordance with the laws of mass-action and equilibrium. There are no energy-relations, but solely the relations of reaction-velocity, concerned in the process. By clearly realizing this fact it is possible to avoid the absurd blunder into which many medical writers fall, namely, that the theory of the reversion of ferment-reactions constitutes a violation of the law of the conservation of energy. The additional objection, frequently stated with pronounced apprehension, that the theory of synthesis by reversion of reaction involves a restriction of the scope of the so-called vital activities of the cells, must unqualifiedly be admitted to be based on fact. This, however, in my humble opinion, is no loss to either biology or chemistry.

The first heading that I have given does not require long consideration. It is not necessary to-day to elucidate the theory of the reversion of chemical reaction. No proposition in theoretic chemistry is more firmly established, and modern treatises practically rest on the flat dictum that all chemical reactions are reversible, if the proper conditions are attained. In the domain of physics the facts are not always so clear. While some of the most exquisite illustrations of reversion are noted in physical reactions (as, for example, in the two forms of crystallization of sulphur), the notion is current that the colloidal reactions are not reversible. A great deal of hasty and immature work has been done on the subject of the colloids; and of no other subject of experimental investigation can it be so emphatically stated to-day that the experimental data lead to conflicting and incongruous inferences. It is clear, however, that included within the so-called colloidal reaction are at least two

factors: purely chemical reactions and the reactions of capillarity, using the term in the strict sense of Willard Gibbs. Now a review of the theory of capillarity does not support the notion that the colloidal reactions are not reversible; that is a purely arbitrary assumption, and is not included in the mathematical formulation of the theory of capillarity. So far as the purposes of this article are concerned, however, this whole matter is quite immaterial; for we shall be concerned almost exclusively with purely chemical reactions. For our purposes, therefore, unlimited use may be made of the physicochemical theory that all reactions are reversible and tend to stations of equilibrium, in which the opposing reaction-progressions are compensated and balanced. In direct analogy to the kinetic theory of gases, we must believe that in chemical systems there is no cessation of reaction, but only the exact counterbalancing of unceasing opposing reaction-progressions.

The demonstration of the occurrence in biologic systems of the reversions that were predicated by theory followed closely on the definite establishment of the theory in the mother science. The experiments *in vitro* have, in many directions, demonstrated such reactions and have attracted widespread attention, because the accomplished reaction constitutes a synthesis. Ten years ago Croft Hill synthesized isomaltose from d-glucose under the action of a vegetable maltase. Since this time isolactose has been synthesized by Fischer and Armstrong; isosaccharose by Wroblewski; while such artificial sugars as tri-acetyl-glucose have been synthesized through ferment-action by Acree and Hinkins. That in all the instances of the synthesis of disaccharids the isomer has been obtained in no wise affects the validity of the result. In the hydrolysis of maltose, lactose and saccharose the iso-sugar appears as the first product of the reaction. Whether the analytical results in the reported experiments are due to the time-factor, the experiments not having been allowed to continue long enough to permit the final product to be found, or whether the stereo-isomeric relations have been the determinants in the outcome, can not now be stated. The synthesis of glucosids, so closely related to the disaccharids in general conformation, has also been accomplished by Fischer. The definite synthesis of a definite polysaccharid has not yet been accomplished. The reported results of the synthesis of glycogen by Cremer, and of starch by Wolff, Fernbach and Maquenne, have not been properly established by indisputable analytical demonstrations. These same reversions may be accomplished with inorganic catalysors, as was shown years before the investigations with the ferments, when Wohl and Fischer synthesized isomaltose from glucose, under the action of sulphuric acid. The fact that when the synthesis is

accomplished under the action of sulphuric acid, the iso-sugar is formed, as is the case with the ferment-reversions, robs this fact of any specific significance.

The synthesis of a monosaccharid, like glucose, from a product of its fermentation, has not been accomplished, nor even rationally attempted. Between d-glucose and its products of fermentation, ethyl alcohol and carbon dioxid, there are at least two known intermediary stages: methyl glyoxal and lactic acid. The formation of the first stage, lactic acid, from ethyl alcohol and carbon dioxid, could not be accomplished except under very high pressure of the carbon dioxid in the system; in the analogous synthesis of sulphuric acid from zinc sulphate and gaseous hydrogen, eighteen atmospheric pressures of the hydrogen were found necessary. The report by Albertson of the synthesis of d-glucose from ethyl alcohol and carbon dioxid under the action of zymase, was not only lacking in analytical foundation, but was devoid of the necessary theoretical basis.

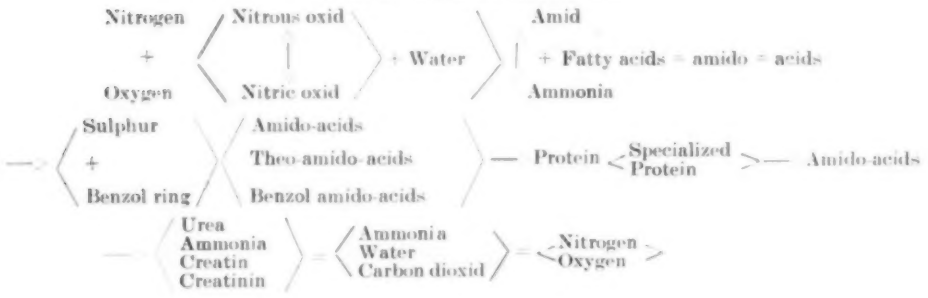
The synthesis of fats through ferment-action was easily accomplished. Almost simultaneously Berninzone and Kastle and Loevenhart synthesized lower esters of the normal series, as did later Hanriot. Later still Pottevin and Taylor were able to form the normal higher fats, using, respectively, the lipase from the pancreas and the castor bean. The structural relations are here very clear. The composition of the products is easily capable of absolute demonstration. Artificial esters can also be found, and apparently the condensation of an alcohol and a fatty acid represents the most feasible illustration of a reversed ferment-action. It must not be forgotten, however, that the autoreaction proceeds here with a demonstrable velocity; so that the condition is one extremely favorable to the demonstration of catalytic or enzymic acceleration. The formation of these fats may also be easily accomplished under the influence of inorganic catalysors.

The synthesis of proteins from amido-acids through the action of ferments has not been accomplished with the ease noted in experiments with the fats and sugars. The investigations of Fischer in the condensation of amido-acids to the so-called peptids indicate that the conditions for the reaction not only are difficult to secure, but must be rigidly maintained. In a word, the synthesis of protein in the laboratory will be much more difficult than was the synthesis of sugar. Years ago a long series of negative investigations was published by Taylor, and Abderhalden has likewise published the details of negative experiments. A year ago I reported the synthesis of protamin, the simple protein occurring in the spermatozoa of fishes, from its component amido-acids, through the

action of a trypsin obtained from the livers of California clams. As the substrate of this experiment, I employed the digested products of protamin. Though the positive results observed in the experiment with the trypsin were not observed in the controls, nevertheless, the experiment lacked the complete validity that could be obtained were the reaction accomplished from the pure amido-acid. This experiment I have since repeated, and I am able to state that by bovine trypsin and by trypsin from the clam, protamin may be synthesized from arginin and the monamido-acids contained in protamin, isolated and purified by the Fischer ester-method.

This leads up to the main subject of inquiry: What are the facts in metabolism that may be logically grouped under a theoretic interpretation resting on the proposition of reaction-reversion? Let us examine, first, the protein metabolism. Chart 1 illustrates the chain of facts in the nitrogen-metabolism in biology.

CHART 1.—NITROGEN METABOLISM.



The formation of the oxids of nitrogen from the gaseous oxygen and nitrogen of the atmosphere is a function fundamental to the lower forms of plant life, and probably also animal life. That these oxids are formed in the air by electrochemical reactions is, of course, certain, but it is equally certain that the reaction, as related to bacterial life, is entirely independent of this; and probably exceeds it largely in quantity. Between the two oxids of nitrogen an equilibrium exists. All bacterial cultures that produce the one produce the other. All bacteria that form nitrite from nitrate also form nitrate from nitrite. Mammalian juices have the same properties.

The next step lies in a combination of water with the oxids of nitrogen and with the production, through reduction, of amid and ammonia. The direct combination of nitrogen with hydrogen apparently does not occur. The nitrogen is first oxidized and then reduced. These reduc-

tions are also the functions of lower vegetable and animal life. Apparently here, also, an equilibrium exists; though, in the attempt to manufacture ammonia from nitric oxid, it has been difficult of definition. Culture experiments on the action of bacteria upon the cyanamids, however, indicate clearly that the reactions are reversible.

The next link in the chain consists in the combination of the amid with fatty acids to form amido-acids. The derivation of the fatty acids will be considered later. This reaction marks a great rise in biologic dignity, and is resident in all the higher plants. While some of the invertebrate forms of animal life are able to subsist on ammonia and amids, the higher forms can not accomplish the synthesis of amido-acids from the fatty acids. The reaction is typically and regularly reversible in vegetable life, as may be seen in the germination of seeds. Plants produce, further, two particular groups of amido-acids, those containing sulphur and those containing benzol. These compounds, indispensable to animal life, can not be formed at all in the higher animal organisms. Man, for example, can not form amido-thio-acids from sulphur in whatever form he ingests the latter; he can not ingest benzol and from it form benzol-amido-acids; for these two special compounds he is absolutely dependent on the plant world.

The final step in the anabolism of nitrogen lies in the condensation of the several amido-acids to proteins. This reaction, most difficult *in vitro,* as the studies of the Fischer school indicate, is apparently accomplished by all plants and animals. While one must not be dogmatic on this point, the experimental investigations indicate that in the dog and the rabbit the nitrogen metabolism may be supported by amido-acids; that is, the organism is able to form protein from amido-acids. From the common protein, typified by serum-albumin, the organism forms the specialized body-proteins, gelatin, myosin, reticulin, hemoglobin, casein, etc., by intramolecular rearrangement of the amido-acid groups. This completes the chain of synthesis. Under the influence of intracellular ferments, the proteins of the body are hydrolyzed to the component amido-acids, and these are then subjected to desamidation, cleavage and further oxidation, the nitrogenous moiety appearing as urea, ammonia, the members of the kreatin-group reactions common in type to all classes of animal and plant organisms. By the action of bacteria these end-products of higher organisms are reduced to gaseous nitrogen, oxygen and water, thus completing the cycle. The two chief differences between the chemical activities of mammals and those of the lower plants lie, on the one hand, in the fact that our organism can not complete the cycle; on the other hand, in the fact that in man the specialization of proteins

reaches a much higher stage. What has been lost in adaptation has been compensated by specialization in synthesis. Man has learned to apply the lesson in this to the world below him; the nitro-bacteria are made to serve the higher plants, just as these plants serve the higher animals.

The entire cycle constitutes a reversion in the physical sense. In the chemical sense, it can be shown that nearly all the individual stages or reactions are capable of reversion in the organism in which they occur. The digestion of proteins is an act of hydrolysis, the proteins being split into their component amido-acids. In this form they are largely, if not entirely, absorbed. While it may be admitted that the products of digestion above the stage of the several amido-acids are, to some extent, capable of resorption, we realize that the velocity of resorption must be a function of the diffusibility of the substance; and, therefore, in the quantitative sense, the state of resorption is unquestionably that of the amido-acids. In the portal vein, the material is to be found largely in the form of common protein. Where has this condensation occurred? Obviously in the intestinal wall. How? The only available and logical interpretation is to predicate a reversion there, under the influence of enzymes. It is, however, not a qualitative reversion; for the particular proteins that were in the diet are not to be found in the blood; only serum-albumin and the globulins are there. Which of these is first formed is not definitely known; but general considerations lead to the inference that it is the serum-albumin that is primarily formed from the products of the digestion of protein, and that from it the serum-globulins are formed. The serum-albumin presents no biologic stamp; the serum-globulins possess specific biologic properties, which we infer were bestowed on them in the conversion from serum-albumin. In all probability there is a relation of equilibrium between these several blood proteins; in any event, the two globulins are known to polymerize in either direction, and the same fact probably holds for serum-albumin and soluble globulin. These blood-proteins are the substrate from which all the specialized proteins are formed. These syntheses are concerned entirely with the groupings of amido-acids, in both the qualitative and the quantitative sense. In general it may be said that the different specialized proteins contain the same amido-acids, but in different amounts, and inferentially in different intramolecular relations. But, in addition thereto, some proteins contain certain amido-acids that are not found in others. Thus some proteins are rich in glycocoll, tyrosin, or thio-amido-lactic acid, while others contain little of these and a few, indeed, none at all. The researches of the Fischer school have given us our first insight into these intramolecular arrangements, and we may expect much

additional light on this subject during the next few years. The reactions of the protein catabolism resemble, in all their chemical details, the tryptic digestion of protein. There is every reason to believe that the autolytic cellular degenerations are carried to the stage of the amido-acids. From these the kreatin, kreatinin, urea and ammonia are derived, and represent in general terms the end-products of the nitrogenous metabolism. To what extent these are correlated in functional, as well as in chemical derivation, is not yet clear. There exists good evidence tending to separate the creatin from the urea metabolism. On the other hand, there is no doubt that kreatin and kreatinin may be converted into urea, just as may uric acid. That the variables in kreatin, kreatinin, urea and ammonia might represent the relations in an equilibrium-system seems to have been overlooked by workers in this subject. The body-juices are able to form urea from ammonia and ammonium carbonate, and ammonia from urea. The equilibrium in this reaction was long ago established by Fawsitt. The body forms urea from amido-acids, but, as far as is known, the reversion of this reaction does not occur in the body. These lower reactions, below the stages of the amido-acids, are not performed by the digestive juices, and in this respect autolysis differs from tryptic digestion. We deal here, of course, with two superimposed enzymic reactions. The fact that urea can be formed *in vitro* from arginin, from monamido-acids and from different ammonia-salts, by animal extracts, removes the entire subject of urea-formation from the domain of cellular physiology, in the older and commonly accepted sense of that term.

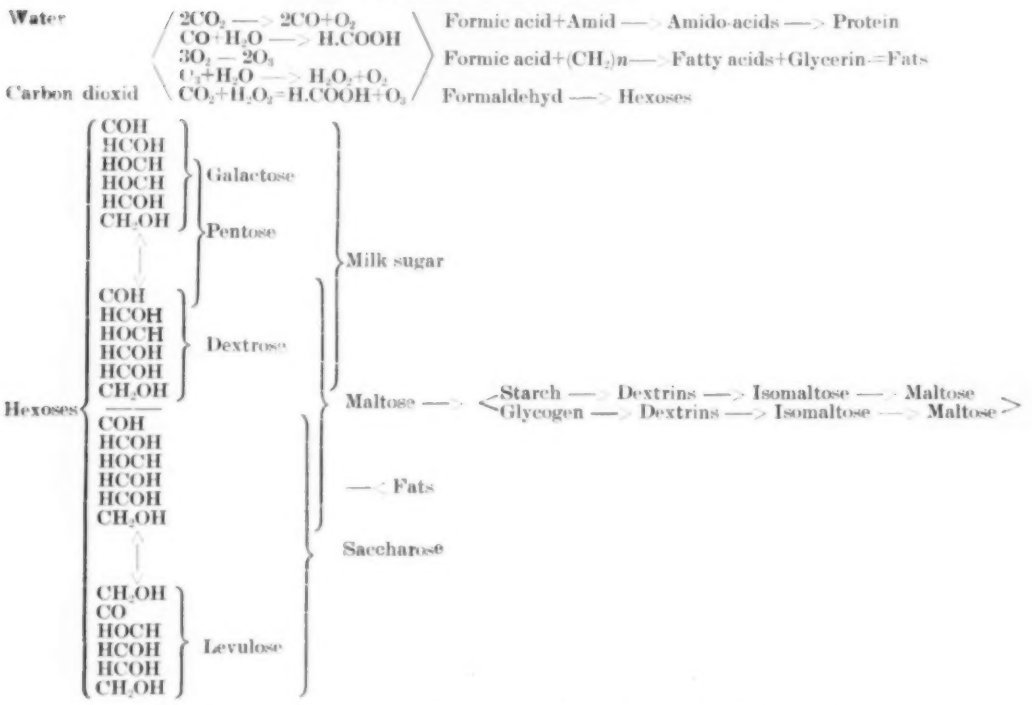
The cycle for the carbohydrate metabolism is shown in the second chart.

The reactions given for the first stages in the reduction of carbon dioxid are drawn from two sources: bacterial investigations and chemical studies on the silent electric discharge. That chlorophyl, in the presence of sunlight, reduces carbon dioxid is, of course, a fact long known. Recent investigations have shown that ozone, hydrogen peroxid and formaldehyd are formed, and the reactions given in the chart represent the most simple and logical way of stating these facts. Loeb's investigations, corroborating the earlier work of Warburg, have shown that the same substances are formed when carbon dioxid is reduced in the electrochemical reaction. When it is recalled that Fischer has synthesized the sugars from formaldehyd, the scheme becomes very impressive. From the formic acid we may naturally predicate the derivation of the various fatty acids, which, combined as amido-acids, are the component of proteins. From formic acid, also, we may, by direct progression in syn-

thesis, rise to the higher fatty acids that form, with glycerin, the natural fat. There can be no doubt that the fats are formed from sugar, and both routes are indicated in the chart.

The reactions up to the stage of the six-carbon sugars occur in all plants and apparently in some of the lowest forms of animal life—unless we cling to the old classification by which chlorophyl absolutely distinguishes plants from animals. Whether the sugars are formed by regular

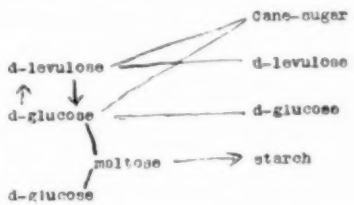
CHART 2.—CARBOHYDRATE METABOLISM.



progression, the hexose from the pentose, is not known, but it is unlikely; while it now seems certain that in the higher animals glucose can be formed from pentose, and *vice versa,* it is certain that in plants the hexoses are not formed through the stage of pentose.

Once the stage of the hexose is attained in plants, most interesting reactions occur. From general evidence it may be assumed that d-glucose and d-levulose, respectively, aldehyd and ketone sugars, are the primary hexoses. These, as first shown by Lobry de Bruyn and Van Ekenstein,

undergo intramolecular rearrangement into each other. Many plants contain d-galactose, in the state of glucosids; and this is, in all probability, derived from d-glucose by intramolecular rearrangement. The relations of equilibrium between d-glucose and d-levulose are varying in different plants and under different conditions. The situation of this equilibrium is complicated by the fact that the two sugars are also undergoing combination to form cane-sugar. In the sugar-beet and in the sugar-cane equal amounts of the two hexoses are formed, and the combination is quite complete, so that the juices of these plants contain largely cane-sugar. In many other plants, the quantities of the two hexoses vary, and the amount combined into the disaccharid varies. Thus, some berries yield largely d-levulose, others d-glucose and little cane-sugar, while other berries contain more d-glucose and much more cane-sugar. Some dates present a large amount of cane-sugar; others contain d-glucose largely, with less of cane-sugar and not a little of uncombined d-levulose. In such plants as form starch, the relations become still more complex, since maltose is being formed from the d-glucose, and from this, in turn, starch. Thus:



Any consideration of equilibrium must needs, therefore, be concerned with five states in a chemical system containing primarily two chemical substances. More than this, the relations vary with time. In the unripe banana, starch is present in predominating amount; as the fruit ripens, d-glucose and d-levulose appear more and more. These combine; so that when fully ripe there is much cane-sugar present. Over-ripe bananas display a marked inversion of their cane-sugar, due, not to bacteria, but to postmortem digestion. It is common in fruits and plants to find the reactions largely in one direction, as to the stage of starch, during the period of growth; while during the period of ripening these reactions are reversed, and the products return to the state of sugar. In the case of the grains and seeds, on the other hand, the carbohydrates remain during the period of ripening, and the reversions occur during the period of germination; but throughout the scene reversions dominate the situation. In another group of plants, reversions occur between fats and

sugar. Thus, in the cocoanut, fat is formed from the sugar during the period of growth; while during the period of ripening sugar is formed from fat. Some of the plant-diseases act through such reversions. Thus, there is a disease of the sugar-cane in which the reversion leads to an excess of primary sugars. There is another disease in which an abnormal polymerization to a dextrin occurs. Both are unquestionably fermentative.

Passing now to the relations in higher animals, similar conditions are encountered. On digestion, starch is hydrolyzed to maltose, and this then to glucose. Maltose can be reabsorbed, as it is readily diffusible; but, since it appears in the blood only as d-glucose, it must have been inverted during its passage through the walls of the digestive tract. Milk-sugar and cane-sugar are also split into their component hexoses during the act of digestion. They, also being diffusible substances, can be reabsorbed; but just as in the case of maltose only d-glucose appears in the blood, so that they must have been inverted during their passage through the wall of the digestive tract. This inversion-function of the mucosa of the alimentary tract has been too often overlooked and constitutes an indispensable factor in the digestion of carbohydrates. Maltose can be hydrolyzed to some extent in the blood and tissues, but apparently cane-sugar and milk-sugar can not be inverted within the tissues, and are eliminated unchanged.

The only glucose to be found in the blood, no matter what the diet, is d-glucose. Therefore, during the act of resorption through the alimentary tract, d-levulose and d-gelactose, components respectively of milk-sugar and cane-sugar, are converted by intramolecular rearrangement into d-glucose; again, without doubt, the reactions of fermentation. These reactions can occur also in the tissues and fluids of the body to some extent. When d-levulose is ingested it is largely utilized; d-galactose, to a much less extent. That the body does not burn d-levulose and d-galactose, can not be stated or proved; but it is much more likely that the body first converts them into d-glucose. In a similar manner it can not be denied that the bacteria of glucose-fermentation act on them; but it is much more likely that they are first converted into d-glucose and then fermented.

The d-glucose is, therefore, the common body-sugar, the substrate of the carbohydrate-metabolism. From it the body forms glycogen, just as plants form starch, and just as the starch is stored until, during the period of its maturation or germination, it is reconverted into sugar, so the glycogen is stored until, the body having drawn on its mass of sugar, it suffers inversion. Without doubt the mass of sugar is the

essential factor; there is a station of equilibrium between sugar and glycogen. When the sugar is augmented by ingestion the reaction proceeds in the direction of glycogen. When the mass of sugar is reduced by combustion the reversed action occurs. Fat is also formed from sugar, and here, too, some such relation of equilibrium must hold, though the situation is not at all clear.

The conversion of d-levulose into d-glucose, which occurs in the mucosa in the alimentary tract, is not reversible in the animal body. The conversion of d-galactose to d-glucose, on the contrary, is reversible, and the reversion constitutes two important physiologic processes. Integral to the central nervous system are combinations of d-galactose with lipoids; the d-galactose is formed in the body, because the growth of the nervous system is not dependent on the presence of d-galactose in the diet, and the blood contains only d-glucose. This (d-glucose) is also carried to the active mammary gland; there in part converted into d-galactose, and combined with an equal mass of d-glucose, to form milk-sugar. If this lactose be then resorbed from the mammary gland into the circulation it can not be utilized or split and is eliminated unchanged.

This brief summary will indicate that in animals, as well as in plants, the carbohydrate-metabolism presents a large number of facts that can be reasonably interpreted only on the theory of reversions applied to fermentative processes.

Coming now to the catabolism of the carbohydrate-metabolism, we may assume that d-glucose is the single substrate of the reactions of carbohydrate combustion within the body. That section of the chart devoted to this portion of the cycle is an adaptation of the scheme of Stoklasa and Bach. It contains the possibly startling assumption that the combustion of sugar in the body passes through the stage of ethyl alcohol.

CHART 3.—CARBOHYDRATE CATABOLISM.

$$\text{Glucose} \longrightarrow \text{Methyl glyoxal} \longrightarrow \text{Lactic acid} < \begin{matrix}\text{Ethyl alcohol} \\ \text{Carbon dioxid}\end{matrix}$$

The scheme is not capable of direct proof to-day. It is based on the following groups of facts: Known bacterial combustions follow the scheme; reactions *in vitro* with ferments follow the scheme; reactions *in vitro* with different methods of oxidation follow the scheme quite closely, and it presents no chemical difficulties, and, lastly, nearly all the substances denominated are known to occur in the normal body, and those not definitely known to occur, are such as are with great difficulty determinable—for instance, the aldehyd. It can not be compared directly

with the scheme for the anabolism of carbohydrates, as there is there a breach between the stage of formaldehyd and that of sugar.

Of this scheme, the only part that concerns us in a discussion of ferment reversion is that above the stage of lactic acid. For reasons before mentioned, a combination of ethyl alcohol and carbon dioxid could not be expected to occur in the body. The reversion from lactic acid to d-glucose can be easily made *in vitro;* and your president, Graham Lusk, has advanced good evidence that it occurs in the body.

Despite the apparent simplicity of the chemical composition of the fats, the steps in their natural synthesis are not clearly understood. Unquestionably, they are first formed in vegetable life by up-building from the lower fatty acids. When fatty acids are formed in the laboratory, one observes an undoubted tendency for them to be formed in series of even carbons. The higher fats occurring in Nature belong largely to the even-carbon series; and the assumption is, therefore, natural, that two $(CH)_2$ groups are added in each step. The formation of the higher fats from carbon and water is the function of all plants, unless we are to assume that in plants the synthesis of the fats may be, instead, via the route of sugar. That in many plants, particularly in seeds and fruits, the reversed reaction, sugar<——>fat—fat<——>sugar, is a prominent reaction, is well known. Whether the higher animals form fats from the lower fatty acids, is not definitely known. If we knew whether, in the formation of fat from sugar, the sugars were first built down to lower fatty acids, we should know from what point in the scale of the fatty acids the animal-organism is able to synthesize the higher fats, but the steps in the conversion of sugar into fat in the animal organism are entirely unknown. The synthesis of glycerin is easily accomplished in both plants and animals. The power of the animal organism to modify higher fats seems to be extremely limited, and this is expressed in the familiar experience that the fats of the diet are deposited in the body unchanged. On the contrary, when the body forms fat from carbohydrate, the species of the animal concerned is of determinate importance. Cattle, horses, dogs and swine will form from the same carbohydrate fats containing very different relative amounts of palmatin, stearin, and triolein. If, however, these four animals are fed fats, these will be deposited unchanged in the tissues. We may formulate this in the terms of the law that body-fat, when derived from ingested fat, is specific to the diet, when formed from carbohydrate, specific to the species.

In the digestion of fats we deal with a simple cleavage. I think it may be stated to-day, without fear of contradiction, that fats are absorbed only after cleavage into glycerin and fatty acids, and not in the form of

an emulsion. In the fluids of the retroperitoneal lacteal circulation the fats are found again recombined. This recombination of the fatty acids and the glycerin must have occurred during the process of resorption through the intestinal mucosa—clearly an act of direct and simple reversion. Following this, occurs a very important condition, which has been generally overlooked. The fat of the body is present in two forms: first, as insoluble neutral fat, represented by the fatty depots of the body; and second, in a soluble state in the circulating fluids, the fat in this instance being in combination with some other unknown component and combination constituting a soluble and diffusible substance. This fact, first described by Connstein, I have been able to verify. It indicates, probably, the following situation:

Depot-fat is storage-fat purely, is not susceptible to any reaction, and corresponds, in the fatty metabolism, to what glycogen is in the carbohydrate metabolism. The active chemical state of fat in the metabolism is the form which is insoluble, diffusible combination. This is the active mass, in the reaction sense, in the fat-metabolism. Between these two conditions an equilibrium must exist. When there is a heavy combustion of fat, reserve fat is transferred to the soluble state; when there is a diminished combustion of fat, soluble fat is transferred to the reserve state.

The combustion of fats within the body is not well understood. Probably in plants fats are never burned, but if utilized are always first reconverted into sugar. For the animal organism, recent chemical work by Dr. Dakin—work of great importance, not only to the physiologist, but likewise to the pathologist—has indicated that when fats are burned they are built down in regular sequences of the even series. That is, stearin is built down to palmatin, etc.; and this condition occurs down to the stage of butyric acid. Unquestionably, the end-products of the fat combustion must be here, again, acetic or formic acid. A decision as to whether the combustion of fats beyond butyric acid passes through the stage of beta-oxybutyric acid, is not essential to the present argument, and the question can not be here discussed. However accomplished, whenever a $(CH)_2$ group is split off and carbon dioxid and water formed, the reaction can not be reversed under ordinary conditions, except under pressure of carbon dioxid. In plants the entire series of reactions may be regarded as reversible; in animals, on the contrary, the scope of the reversions is comparatively narrow. In the animal body, fat is formed from sugar. Whether this reaction is reversible, and whether in the animal body sugar is formed from fat (as asserted by Pflüger), can not now be decided. There can be no question that the view of Pflüger is

very attractive; it offers a simple, natural and logical explanation for some of the most difficult situations in chemico-physiology, and is supported by the analogy in the vegetable kingdom. It is, however, devoid of any direct demonstration.

In the purin-metabolism we deal with what chemically is probably the most complicated of the functions of the body. Nuclein contains, as you will recall, a pyramidin-body, purin-bodies, pentose, and phosphoric acid. It is firmly established that the body needs none of these in the diet, except, of course, phosphoric acid. The egg contains, practically speaking, no purin, pyramidin, or pentose; but the embryo contains in its nuclei large amounts. Obviously, therefore, the growing organism is able to synthesize all these; and to the great biologic importance of this synthesis the recent researches of Jacques Loeb have given emphasis. Chemically, it is certain that pyramidin and purin may both be formed from amido-acids, so that the substrate for their derivation is abundantly present in the proteins of the body. Pentose is undoubtedly formed from glucose—a reaction that may be easily accomplished in the laboratory. These are then combined by reduction and anhydration, to form nucleinic acids, which enter into combination with protein. When nuclein is ingested it is split, in the act of digestion, into its component groups. In all probability these are never utilized in the synthesis of the body-nuclein. In a word, the animal organism is not only independent of ingested nuclein from animal or vegetable food, but is probably unable to utilize purin, pyramidin, and pentose furnished to it through the alimentary tract. Exogenous purins and pyramidin and pentose are either burned or eliminated *in toto*. In other words, the digestive reaction of cleavage of nuclein is not reversible in the body. The synthesis apparently follows other lines. In the death of the cell the nuclein contained in its component parts is split, and the pentose, purin, and pyramidin are eliminated or burned. In other words, the waste products of nuclein-metabolism are, like the products of nuclein-digestion, of no further utilization in the body. In this metabolism, therefore, we have apparently no illustrations of a direct reversion in the animal body. In the larger sense, however, we have one illustration of such a reversion. The ripe egg of fishes, as first shown by Meischer, contains no nuclein. The unripe egg, however, does contain nuclein in its protoplasm. On hatching, the embryo, of course, contains nuclein. With the ripening of the egg there is a disappearance of the nuclein; with the germination of the egg, a reappearance of the nuclein—and all within the same minute organism. Here, therefore, we have an illustration of a reversion

in the purin-metabolism. In the matured animal organism, however, we have none.

These general remarks illustrate clearly, I believe, the fact that reversions constitute some of the most important and indispensable chemical reactions occurring in animals, as well as in plants. A few points only require further elucidation.

To what shall we attribute the reversions? To ferments, undoubtedly. To what ferments? There is a growing unfortunate tendency in biologic literature toward a multiplication of the ferments. For this the terminologic practices of the Ehrlich school are in part, no doubt, responsible. As you are aware, when Ehrlich encounters a difficulty he is inclined to invoke a new force to explain it. Thus early in the investigations on diphtheria poison he assumed in diphtheria toxin the presence of but two or three substances, in order to explain all the apparent experimental facts. As the experimental facts have increased, this number has been amplified, until now more than a dozen hypothetical substances are assumed to be necessary to explain the facts. If this doctrine were applied to the ferments we should soon have an uncountable number of ferments, each acting in an infinitely small capacity. We know, for example, that in many of these reactions there are many intermediary stages. If we are to assume a specific ferment for each stage, we shall soon be in hopeless confusion. For example, between glucose and alcohol, we have certainly methyl glyoxal and lactic acid, and probably one other stage. According to this use of the concept "ferment" we might assume four ferments to be necessary for alcoholic fermentation. Now, considering the general chemical principles that (1) in a series of reaction-progressions the first stage produced is not to the final, but to the least stable, stage, and so on until the final stage is reached; and (2) that this series of intermediary reactions in no wise affects the chemical conception of reaction as related to the mass of the primary reacting bodies; it is clear that this tendency to the multiplication of ferments must be resisted, if clarity is to prevail. Platinum black can form alcohol from sugar; and there is no reason why zymase should not do it just as well. A more serious blunder is being made in the assumption that in the reversions other ferments are concerned, that one ferment forms sugar from glycogen, and a different ferment forms glycogen from sugar. Now to the physicochemist, this is a complete nullification of the argument. If a ferment can not work in both directions, it can not work in one direction. The ferment simply accelerates the velocity of the reaction that is progressing toward the station of equilibrium, irrespective of the direction in which the station of equilibrium lies. The lubrication of the bearings

of a locomotive reduces the friction, and, therefore, increases the speed of the locomotive, irrespective of whether it is going forward or backward. The assumption that ferments can work only in one or the other direction involves a complete collapse of the theory of catalytic acceleration of reaction, and is absolutely untenable according to the modern conceptions of the physical and chemical sciences.

Lastly, one extremely interesting theoretical consideration remains: the mechanism by which the conditions of reversion are accomplished. Nitrogen and oxygen will not combine in air, except in infinitesimal quantities, because of the low temperature. As the temperature is raised, the station of equilibrium is shifted in the direction of the oxids of nitrogen. When, as occurs to-day in the commercial manufacture of these oxids, an arc-discharge is passed through a current of air, with the production of these oxids, we are dealing with a thermochemical reaction. At the high temperature produced in the discharge of the arc, nitrogen and oxygen combine; the station of equilibrium is shifted in their favor, and the velocity of combination is increased. Unless these oxids are promptly combined, before cooling occurs, dissociation will take place. In the formation of the oxids of nitrogen in plants and bacteria, on the other hand, no such temperature factor can be invoked. Here some other factor intervenes to shift the station of equilibrium. What is this factor? We do not know.

A somewhat analogous consideration holds in the reduction of carbon dioxid. Chlorophyl, in the presence of sunlight, is able to reduce carbon dioxid to formaldehyd—a reaction that does not occur in appreciable amount at ordinary temperature, in the presence of either chlorophyl or sunlight alone, when carbon dioxid and water are in contact. Here we are dealing with a photochemic reaction, the effect of which is again to shift the station of equilibrium in the direction of the product of combination. The same thing occurs in the silent electrical discharge, as illustrated in the equations of Walter Loeb—unquestionably here, however, not photochemic in nature. In plants the formation of stereo-isomeric sugars must be associated in some way with the presence of circumpolarized rays in our solar light. Theoretically, in the reversion of such reactions, the stereo-isomeric influence must be a factor. These considerations apply, of course, to the physiology of all organisms, animal and plant. Undoubtedly, the reduction of carbon dioxid and the formation of the sugars are photochemic reactions purely, whether they occur in plants or in animals. The formation of the oxids of nitrogen, on the other hand, and of the building-stones of protein, is not photochemic, nor is it thermochemic. A few years ago Engelmann published

a calculation designed to show that at the instant of chemical combustion within the cell extremely high temperatures are developed. Even granting the entire argument, however, I do not believe that this fact could be utilized to explain the association of nitrogen and oxygen in the bodies of bacteria.

In the reversions that are known in higher organisms, what constitute the general conditions? According to the laws of general chemistry, the conditions determining the station of equilibrium are the temperature, the concentration of the total system, and the mass of the reacting bodies. These are, in part, operative, of course, and can be used to explain many of the phenomena. When sugar is burned by violent exertion the mass of sugar in the body becomes reduced, and, of course, the reversion-reaction, glycogen to sugar, becomes stimulated. There are, however, reversions in which these will not hold. We are not able, by the variation of the known chemical factors, to determine the station of equilibrium as they are observed in physiology. In the purely chemical system the mass of the catalysor is not a determining factor; in the ferment systems, however, it is a determining factor. The station of equilibrium depends on the temperature, the total concentration of the system, the masses of the reacting bodies and their products, and the mass of the ferment. We are able *in vitro* to show an influence on the station of equilibrium due to the mass of the ferment. We are not able *in vitro*, however, even with this factor, to explain the remarkable reversions that occur within the body; nor are we able to account for the velocity of the reversions. The body accomplishes in a few hours what the most painstaking experiments will not accomplish in weeks. There are apparently present in the living body, but not yet attained in our experiments, conditions involving the station of equilibrium and the velocity of the reaction that determine the marked difference between the results of Nature and those of the laboratory. That these as yet unknown factors are purely chemical or physical must, of course, be believed. While, therefore, we know of the rôle of reversions in the body, that is, that such and such reactions constitute reversion and occur in the body, what we do not fully appreciate or understand is the velocity with which the reactions that can be accomplished without, as well as within the body, occur within it.

BLOOD-PRESSURE-LOWERING REFLEXES FROM IRRIGATION OF THE CHEST IN EMPYEMA.*

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In a previous paper[1] some experimental work was published, in which it was shown that irritation of the pleura by mechanical or chemical means would sometimes give rise to a reflex fall in blood pressure. It was shown also that this depressor reflex occurred more frequently when the irritant was applied to the inflamed pleura than to the normal pleura.

These results suggested the possibility of danger in the treatment of empyema by irrigation with antiseptic solutions. In order to determine how great this element of danger is, the following irrigation experiments were carried out on healthy dogs and on dogs with artificial empyema.

To produce empyema a few ounces of contaminated cotton-seed oil are injected into the pleural cavity of a dog. After forty to fifty hours the animal is languid and feverish. Examination of the thorax shows on the side injected an abundant seropurulent exudate and, as a rule, a rich deposit of fibrin over the visceral and parietal pleuræ. These conditions are thus seen to be very similar to those found in the early stages of empyema in man. In the other pleural cavity is usually seen a thin fibrinous exudate with little or no free fluid.

In the following experiments from 50 to 100 c.c. of the free fluid exudate was siphoned off, then 50 c.c. or less of the test fluid injected. In this way any disturbance of blood pressure from pressure of fluid on the lung was excluded. Furthermore, the irrigating fluid was withdrawn at once to prevent undue absorption.

IRRIGATION WITH HOT WATER.

Of four normal dogs in which hot water was used for irrigation of the pleural cavity, one showed a rise in blood pressure of 20 mm. Hg.; the other three no change. Of six empyema dogs similarly treated, three exhibited a moderate rise in pressure and three no noteworthy change. The tendency of hot water, therefore, is to elevate blood pressure to a very moderate degree.

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* From the Laboratory of Experimental Therapeutics, University of Chicago, S. A. Matthews, Director.

* Read at the meeting of the Association of American Physicians at Washington, D. C., May, 1908.

1. Jour. Am. Med. Sci., December, 1907.

IRRIGATION WITH COLD WATER.

In one of three normal dogs washed out with cold water there was a fall in blood pressure of 30 mm. Hg.; in the other two very little fluctuation occurred. In two of five empyema dogs irrigated in the same way a slight fall in pressure took place, while in three no effect was apparent. A rise in blood pressure after using cold water was not obtained. Hence the tendency of cold water is to slightly depress blood pressure.

IRRIGATION WITH FORMALIN AND GLYCERIN.

The solution employed was formalin, 2 per cent., in glycerin. Two of eleven normal animals treated with the above solution gave a considerable fall in blood pressure, one a moderate rise, and eight no appreciable change. Of thirteen empyema animals irrigated in like manner, six showed a marked fall in pressure varying from 10 to 100 mm. Hg., and the others little or no variation.

A considerable fall in blood pressure took place in 18 per cent. of the normal dogs, in contrast to 40 per cent. of the empyema dogs. Moreover, the average fall was much greater in the empyema dogs than in the normal dogs.

IRRIGATION WITH IODIN SOLUTION.

The fluid was Lugol's solution so diluted as to contain 1 per cent. of iodin. In one of the six normal dogs washed out with this solution a moderate fall in blood pressure followed; in five dogs the effect was nil. In two of eleven empyema dogs thus treated a marked but transitory fall occurred; in nine dogs no change was apparent. The iodin solution only exceptionally produced any depressing effect on the blood pressure and never endangered the animal's life.

IRRIGATION WITH HYDROGEN PEROXID.

Especial care was taken in this series to aspirate fluid and gas immediately after the hydrogen peroxid was introduced in order to avoid compression of the lungs.

Irrigation in two of the nine normal dogs was followed by a moderate fall in blood pressure, no especial variation being recorded in the remaining seven. Similar treatment in sixteen empyema dogs was followed in eleven by decided falls in blood pressure varying from 25 to 150 mm. Hg. In several instances the pressure fell to zero. In one case a fatal fall was preceded by a rise of 40 mm. Hg.

The depressor reflex was elicited in 70 per cent. of the empyema dogs, as compared with 22 per cent. of the normal dogs. Furthermore, the reflex was more severe and dangerous in the empyema group.

In dogs that had previously been washed out with hot water the pressure was less likely to fall. This may be explained by the fact that in the presence of pus the hydrogen peroxid induces a more rapid release of oxygen gas and is consequently more irritating.

RESPIRATORY CHANGES.

Associated with the depressor reflexes of blood pressure in the preceding experiments there was a tendency on the part of the respiration to become slower and more shallow. The change in breathing, as a rule, was simultaneous with that in the blood pressure, which suggests that the disturbance of both functions was due to the same cause, and not one a result of the other.

CAUSES OF FALL IN BLOOD PRESSURE.

There are three possible explanations for the fall in blood pressure incident to these pleural irrigations, namely, absorption of substances that have a depressor action, compression of the lung, and direct irritation of nerve endings.

1. Absorption of fluid by the blood with resultant action on blood pressure can not explain the phenomena for these reasons: *a*. The fall often follows the introduction of fluid in a few seconds—an interval that is too short for any appreciable absorption to take place. *b*. As the antiseptic solutions were drawn off as soon as injected, the small amount of remaining fluid, even if absorbed, would not be sufficient to cause any appreciable change in blood pressure. *c*. All these solutions, in similar quantities, when injected into the peritoneal cavity, caused practically no change in blood pressure.

2. Compression of the lung and restriction of the respiratory capacity can also be eliminated as a cause of the fall in blood pressure, because not more than 50 c.c. of the fluid was introduced at one time and most of this was removed immediately. In previous experiments we found that 100 c.c. of a non-irritating fluid, such as oil, could be injected into the pleural cavity without influencing materially the blood pressure. As stated before, special precautions are necessary to allow the escape of gas when using the hydrogen peroxid for irrigation; otherwise the compression of the lung might have a considerable influence on blood pressure.

3. Irritation of the nerve endings in the tissues lining the pleural cavity is the only reasonable explanation of the blood pressure disturbance. In previous experiments with empyema dogs we have been able

in a certain proportion of cases to elicit depressor reflexes by applying a few drops of strong formalin or mustard oil to the inflamed pleura. The rapid onset of the fall in blood pressure, the frequency of transitory falls with complete recovery, and the accompanying shallowness of respiration are characteristic of such a reflex.

ORIGIN AND SOURCE OF REFLEXES.

Nerve endings in the visceral and parietal pleura and perhaps sympathetic nerve fibers in the immediate vicinity carry afferent impulses to the vasomotor and respiratory centers in the medulla. Thence efferent impulses may be reflected to the heart, the lungs and the systemic blood vessels. *A priori* we should expect such afferent impulses to cause either a pressor (excitor) or a depressor effect on the circulation. In our experiments we did obtain in some instances a pressor effect from hot water, but not often from the antiseptic solutions. From the latter the disturbance was almost always of a depressor kind. Whenever the depressor reflex was marked a slow and shallow respiration developed, indicating a combined influence on blood pressure and respiratory centers.

The reflex was usually of the vasomotor type and not prevented or materially modified by atropin. Adrenalin, administered intravenously, and artificial respiration were the most efficient means of restoring blood pressure.

Section of the cervical vago-sympathetic nerves in some animals prevented the reflex, and at times brought about recovery after the blood pressure had fallen. In other animals section of these nerves had little or no influence.

The inference to be drawn from these facts is that afferent impulses travel to and efferent impulses from the medulla through the vago-sympathetic nerves; when, however, these nerves are divided in the neck there is evidence that impulses may be conducted in both directions through the spinal cord.

CLINICAL BEARING OF EXPERIMENTS.

That collapse and even death have occurred in empyema during irrigation of the pleural cavity with antiseptics is abundantly proved by the literature and by unpublished experience of physicians, but the cause of these accidents has not been understood. It must be admitted, however, that such accidents are infrequent compared with their frequency in our experiments. This difference between experimental and clinical results is probably due to the different degree to which the pleura is exposed to irritation. In the recently produced empyema of dogs the fibrinous exu-

date is not sufficiently thick and uniform to cover and protect the pleura, whereas in the older empyemas of man the fibrinous exudate is usually dense enough to protect the pleura from irritation. It is reasonable to suppose that in those instances in which collapse occurs in man the protective exudate may be too thin, or that certain areas of the pleura may have been exposed by removal of fibrin.

SUMMARY.

1. Irrigation of the pleural cavity with various solutions may induce either a pressor (excitor) or depressor influence on the arterial circulation. Of the two influences the depressor action is the more frequent and of greater clinical importance.

2. Comparing the effect on the blood pressure of healthy dogs with that of empyema dogs, when a given solution is used for irrigation, we conclude that the tendency to reflex disturbances is the same in kind, but that the frequency of the reflexes and their severity is much more marked in the empyema dogs than in the healthy animals.

3. *a*. Hot-water irrigation has a tendency to elevate blood pressure slightly.

b. Cold water tends to lower blood pressure to a slight degree.

c. Lugol's solution occasionally produces a marked fall in blood pressure, but the effect is transitory.

d. Formalin (2 per cent.) in glycerin often sets up a depressor reflex, and this is sometimes dangerous to life.

e. Hydrogen peroxid is seldom a menace to normal dogs, but is frequently so to those with empyema. Death may ensue even when the gas is allowed to escape.

4. The comparative rarity of depressor reflexes during irrigation of empyema in man, as compared with those occurring in animal experiments, is probably due to the fact that in the old empyemas of man the pleura is usually protected by a thick fibrinous exudate. This protection, however, can not be relied on, and, therefore, the practice of irrigating the pleural cavity with antiseptic solutions is not free from danger.

5. Adrenalin administered intravenously helps to restore blood pressure, but its action is not lasting. Artificial respiration by intermittent positive pressure is the most reliable means of restoring and maintaining blood pressure, and also exerts a powerful preventive influence on the depressor nerves. As long as air is regularly and intermittently forced into the lungs under moderate pressure, depressor reflexes are not easily elicited by irritation of the pleural nerve endings.

100 State Street.

A STUDY OF THE VOLUME AND SPECIFIC GRAVITY OF ORGANS.*

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The three linear dimensions in which the size of an organ examined at autopsy is recorded give to the reader a rather indefinite idea as to the actual size of the specimen. Viscera are irregular. The expressions "the organ is large," "fairly large," "voluminous," "larger than its fellow," "contracted," "splenic tumor," etc., are inaccurate and unscientific.

In order to determine and accurately register the size of any viscus, the following plan, employed at some institutions for registering the volume of the brain, should be adopted: Each organ as it is removed is submerged in a vessel filled with water to a level at which an overflow is provided. The water displaced overflows into a container graduated in cubic centimeters; the amount so obtained represents the volume or displacement of the organ in cubic centimeters. The organs are weighed in grams; the weight, divided by the displacement, equals the specific gravity.

The heart is submerged opened or unopened. A "voluminous" emphysematous lung is pressed beneath the surface of the water by a rod thrust into the bronchus. It has been ascertained that no water enters the lungs—no bubbles appear because the contained air can not be displaced. The liver, spleen, kidneys or any tumor may be similarly measured. The record is thereby supplied with definite facts by which it is possible to appreciate the size of an emphysematous lung as compared with its atelectatic mate. The displacement in cubic centimeters constitutes a record, conveying an idea not obtainable from linear measurements even where the weight also is given.

Dr. L. Vervaeck, of Belgium, determined the specific gravity of organs and published his results in 1901. The method he used requires two weighings, one in and one out of water. His tabulations were based on the general clinical diagnosis of the case and not on the pathologic condition observed in each organ. The specific gravity of the lungs was not determined.

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*From the Laboratories of the Jefferson Medical College Hospital. Read before the Pathological Society of Philadelphia, March 12, 1908.

In order to determine the practical value of the methods suggested I examined the organs from one hundred postmortems made at the Philadelphia Hospital.[1]

HEART.

While the average specific gravity of hearts manifesting no evident abnormality was 1029, individual apparently normal hearts varied from 939 to 1152. It is not likely that healthy heart muscle varies in specific gravity to the extent indicated. Any marked deviation from the normal specific gravity, in a heart macroscopically normal, indicates that a histologic study is necessary. In cloudy swelling—eight cases—the average specific gravity was found distinctly lowered, namely, to 1004. This conforms to observations made during the study, namely, that parenchymatous change lowers the specific gravity of the affected organ. In so-called chronic myocarditis, including general atrophy (twenty cases) the average specific gravity was 1008; lowest 833; highest, 1088. Hypertrophied and dilated hearts (thirty-one cases) yielded an average specific gravity of 1037; lowest 969; highest 1114. In simple hypertrophy (thirteen cases) the average specific gravity was 1032; lowest 975; highest 1128. Comparing hypertrophy with hypertrophy and dilatation combined, the previous observations seemed again to hold true. In dilatation, failure of nutrition and parenchymatous degeneration, the specific gravity was, as a rule, lower than in simple hypertrophy. The same general tendency obtains in chronic dilatation and fatty degeneration. Here with even greater parenchymatous change (twelve cases) the average specific gravity is still lower, namely, 1025; lowest 843; highest 1214. Fatty infiltration presents a contrasting picture. Here with an intact musculature the specific gravity remained high, the average of five cases being 1061; lowest 1000; highest 1151.

KIDNEY.

The average specific gravity of the normal kidney (only eight such available) was 1098; lowest 1000; highest 1190. In acute diffuse nephritis (twenty kidneys) the average specific gravity was lowered to 1072.

In chronic parenchymatous nephritis (103 kidneys), commonly a diffuse lesion, the average specific gravity was further lowered, 1049. In one case the right kidney had a specific gravity of 1400. The left kidney was less granular; accordingly its specific gravity was only 1200.

1. The notes of the cases studied may be found in the Philadelphia Hospital records, 1906, xxi.

In chronic interstitial nephritis (fifty-eight kidneys) the average specific gravity, 1053, was higher than in chronic parenchymatous nephritis. As illustrating the influence of morbid processes in the displacement—size—of the organ, a comparison of the average volumes of the kidneys is interesting and suggestive.

Average volume, chronic interstitial nephritis (58 cases).....150 c.c.
Average volume, apparently normal kidneys (8 cases).....160 c.c.
Average volume, chronic parenchymatous nephritis (103 cases)...166 c.c.
Average volume, acute diffuse nephritis (20 cases).....185 c.c.
Average volume, acute diffuse nephritis and congestion (8 cases).186 c.c.

While parenchymatous change seems to lower the specific gravity of the organ, the formation of fibrous tissue, on the other hand, raises it. This is perhaps best indicated by examination of the kidneys in chronic interstitial nephritis. Assuming that the kidneys of the smallest volume have undergone the most interstitial change—are most fibrous—the following comparisons may be made.

8 kidneys chronic interstitial nephritis, vol. 100 c.c. or less, av. sp. gr. 1257.
42 kidneys chronic interstitial nephritis,* vol. 100 to 200 c.c., av. sp. gr. 1025.
8 kidneys chronic interstitial nephritis,† vol. over 200 c.c., av. sp. gr. 994.

The organ becomes more dense because it contracts. The increased specific gravity contributed by fibrous tissue formation is not demonstrable in every case, be it heart, liver, or kidney, because fibrous or interstitial processes are rarely dissociated from parenchymatous change. Where fibrosis is most marked, as in the group of small kidneys in chronic interstitial nephritis, the consequent increase of specific gravity is best illustrated.

LIVER.

In organs not the seat of any macroscopically evident lesion (eleven cases) the average specific gravity was 1057; lowest 1029; highest 1088. The specific gravity is lowest in fatty infiltration of the liver (twenty-one cases); average 1028; lowest 1020; highest 1098. In cloudy swelling, parenchymatous degeneration (twelve cases) the average specific gravity was 1055; lowest 1025; highest 1086. In atrophic cirrhosis (seven cases) the average specific gravity was 1056; lowest 1029; highest 1069. In congestion amounting to red atrophy, average specific gravity was 1077; lowest 973; highest 1100.

* Probably less fibrous. †Probably least fibrous.

SPLEEN.

Except in miliary tuberculosis the average specific gravity of the spleen is highest in chronic splenitis (twenty-eight cases), 1139, succeeded in order by the following: Acute splenitis (nineteen cases) 1110; congestion (nineteen cases) 1108; apparently normal (thirty-three cases) 1043; acute suppurative splenitis (two cases) 1040; amyloid (three cases) 1027.

LUNGS.

As regards the lungs this method offers a more perfect mode of comparison of size of the two organs than can be obtained in any other way. In support of this statement the following cases may be cited:

CASE 38.[2]—Patient aged 26; right lung, weight 460, vol. 850, sp. gr. 541; chronic caseous tuberculosis; left lung, weight 780, vol. 770, sp. gr. 1013; chronic caseous tuberculosis and atelectasis of lower lobe.

It is clear in this case that the right was the functionating lung; less weight, greater displacement, lower specific gravity.

CASE 39.—Patient, aged 35; right lung, weight 590, vol. 810, sp. gr. 728, edema and congestion; tuberculosis of lower lobe, hence higher specific gravity. Left lung, weight 400, vol. 640, sp. gr. 625; edema and congestion.

CASE 53.—Patient, aged 57, right lung, weight 560, vol. 580, sp. gr. 965, emphysema, congestion, healed tuberculosis; left lung, weight 190, vol. 180, sp. gr. 1055, atelectasis.

No description could give as adequate an idea of the conditions in this case as the figures quoted.

CASE 76.—Patient, aged 24; right lung, weight 460, vol. 670, sp. gr. 686, acute miliary tuberculosis. Left lung, weight 460, vol. 610, sp. gr. 754, acute miliary tuberculosis.

The two lungs weighed the same; the right lung was larger; the left should have weighed less; the specific gravity of the left was the higher. From the figures alone it is proper to conclude that the left lung was the more involved.

CASE 88.—Patient, aged 46; right lung, weight 660, vol. 1200, sp. gr. 500, emphysema. Left lung, weight 940, vol. 1300, sp. gr. 723, lobar pneumonia involving part of upper lobe; the remainder of the organ emphysematous.

CASE 108.—Patient, aged 50; right lung, weight 540, vol. 1150, sp. gr. 469; the organ apparently normal, crepitating throughout; left lung, weight 1790, vol. 1780, sp. gr. 1005, lobar pneumonia; nowhere crepitant.

These few cases are sufficient to illustrate what is already known, namely, that conditions like fibrosis, atelectasis and pneumonia, increase the specific gravity of the lung. Comparison of weights, volumes and specific gravity of the two lungs gives an approximate idea of the amount of functionating tissue present in each.

2. Weight is given in grams and displacement, or volume, in cubic centimeters.

CONCLUSIONS.

A statistical study of the organs of 100 consecutive autopsies seems to indicate:

1. Parenchymatous degeneration lowers the specific gravity of organs proportionately to the degree of parenchymatous change.

2. Fibrotic change, while diminishing the volume of the organ, also raises its specific gravity proportionately to the amount of fibrosis.

3. Although useful in systematic studies of all organs, the specific gravity records are most striking in pulmonary affections.

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THE OCULAR TUBERCULIN REACTION.

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AND

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About a year ago Wolff-Eisner[1] in Berlin, and Calmette[2] in Paris, published almost simultaneously articles on the use of tuberculin in the eye as a diagnostic aid in the treatment of tuberculosis.

Since that time the work has been reviewed and repeated by many, both clinicians and pathologists, with considerable divergence of opinion as to its value. Therefore, it seems well to add to the literature any considerable number of cases.

The use of hypodermic injections of old tuberculin (Koch) for diagnostic purposes has been well tested for a number of years and its advantages and limitations are fairly well understood. Chief among the latter have been its inapplicability in pyrexial cases and the general malaise and discomfort attending a positive reaction. Most important among the former were the local reactions around the tuberculous focus, be it a joint or an apex of a lung. It is obvious that a method producing the same results, which could be used in febrile cases and which would be free from attendant discomforts, would be of enormous advantage. It is with this expectation that one turns to the conjunctival reaction.

The method in itself is simple. A solution of Koch's old tuberculin is precipitated with 95 per cent. alcohol, the filtrate washed with 70 per cent. alcohol to free from glycerin, dried and redissolved in sterile normal salt solution, in the required strength. Wolff-Eisner advises the use of old tuberculin in 1 per cent. solution. In our cases the method advised by Dr. Baldwin[3] was employed. Through the kindness of Drs. Trudeau, Baldwin and Levine, of the Rockefeller Institute of New York, we were supplied with requisite tuberculin in the dried form, which was then made up in 0.5 and 1 per cent. solutions and placed in sterilized glass tubes containing sufficient for ten doses. Baldwin's throttled

1. Wolff-Eisner: Berl. klin. Wchnschr., 1907, xliv, 703; Beitr. z. Klin. d. Tuberk., 1907, ix, 1.
2. Calmette: Presse méd., 1907, xv, 388, 443.
3. Baldwin: Jour. Am. Med. Assn., 1907, xlix, 1969.

eye-dropper was used in order to deliver a measured drop (0.025 c.c.) and so secure uniformity of dosage.

Our method is the following: Both eyes are first inspected for possible pre-existing difference. The lower lid of the right eye is everted, best with the patient in the reclining position, and the drop instilled into the inner canthus. Care should be observed to close the eye for a full minute after the instillation to prevent the drop from being expelled or winking or lachrymation, and also to insure prompt application to all points of the conjunctiva. Children who are readily frightened and weep copiously may wash the tuberculin from the eye, thus making the dosage an infinitesimal fraction of the amount instilled. This point will be commented on later. A certain proportion is in any case lost through the lachrymal duct.

A reaction is readily appreciated by comparing the instilled eye with the normal. Dr. Baldwin's scheme was adopted in the main as follows:

Negative: No difference in color when lower lids are pulled down and compared.
Doubtful: Such difference in caruncle and conjunctiva that one is scarcely certain it exists.
+: Distinct palpebral redness and secretion.
++: Ocular and palpebral redness and well marked secretion.
+++: Deep injection of entire conjunctiva with edema of the lids, photophobia and secretion.

The reaction, if positive, usually begins in four to six hours, is at its maximum in twenty-four hours, remains so for perhaps another twenty-four hours, and then gradually subsides until at the end of three or four days no trace of the reaction remains. Observations were regularly made at the end of six, eighteen, twenty-four, forty-eight and sixty hours. The subjective feeling in the case of a + reaction is practically nil, amounting at the most to a slight sandy feeling. With the ++ reaction there is a distinct foreign-body feel, while with the severe reaction there is a real discomfort. In none of our cases, however, was an extremely severe reaction experienced. Dr. F. J. Parker examined the eyes of about forty patients and found no change except in the conjunctiva.

For comparison we here append a few of the results of other observers:

Wolff-Eisner[1]—Pulmonary Tuberculosis.	Positive.	Negative.	Doubtful.	Per Cent. Positive.
First stage	14	6	..	70
Second stage	15	11	..	57
Third stage	5	13	..	39
Baldwin[5]—Pulmonary Tuberculosis.				
.....	42	2	1	93

SMITHIES AND WALKER[4]—PULMONARY TUBERCULOSIS.				
.....	9	2	..	82
SMITHIES AND WALKER[4]—JOINT TUBERCULOSIS.				
.....	18	1	..	95
CALMETTE[5]—TUBERCULOSIS.				
.....	62	..	..	100
CALMETTE[5]—SUSPECTED TUBERCULOSIS.				
.....	..	..	2	..
FLOYD AND HARRIS.				
.....	28	13	6	59

In our experiments 166 patients were tested. Nearly all were patients at Seton Hospital in our services.

FIRST GROUP.

	Positive.	Doubtful.	Negative.	Total.
Non-tuberculous	..	..	8	8
Adenitis, two cases.....	1	..	1	2
Genitourinary suspects	..	1	2	3
Pulmonary suspects	8	1	13	22
Skin lesion, solitary tubercle	1	..	..	1
				36

Of this group eight were tested with injections of tuberculin, 0.001 gm. and 0.002 gm. with negative result. In every case the conjunctival reaction was also negative. One patient reacted to an injection of 0.002 which showed the conjunctival reaction +++. Of the genito-urinary patients, one that reacted negatively to a 1 per cent. solution and was negative also to tuberculin injection of 0.002 gm. was proved to be tuberculous by the injection of the urine into a guinea-pig which later developed tuberculous lesions.

SECOND GROUP.

Tuberculous Cases.	Positive.	Negative.	Doubtful.	Per Cent. Positive.	T'l's.
1. Incipient lesions of one apex or lobe...	17	5	..	73	22
2. Moderately advanced	20	7	5	63	32
3. Advanced and far advanced.....	27	9	5	64	41
4. Orthopedic	21	6	6	64	33

In these cases only a 0.5 per cent. solution was instilled into the eyes of forty-six patients, twelve of them being negative and not retested (four clinically non-tuberculous). Of the remainder, eighty-six were tested with a 1 per cent. solution alone, and the rest were tested twice. Thirty-four cases were twice tested with the following rather remarkable results:

4. Smithies and Walker: Jour. Am. Med. Assn., 1908, I, 259.
5. Floyd and Harris: Jour. Med. Research., 1908, xvii, 495.

THIRD GROUP.

Negative to both 0.5 and 1 per cent. solutions	12
Positive to the second instillation of 1 per cent., negative to 0.5	9
Positive to both (a) stronger with 0.5	1
(b) stronger with 1 per cent	1
(c) stronger to second of 1 per cent	1
Positive to 0.5, negative to 1 per cent	6
Doubtful to both	2
Negative to first, doubtful to second	2
	34

Several facts at once appear which require explanation. That nine patients should react to a stronger solution after failing to do so with a weaker, seems to require no comment; but that six patients reacting to an instillation of 0.5 per cent. should be negative to a stronger solution is a fact seemingly contradictory. Its explanation depends perhaps on several factors: First, a considerable time elapsed, in several cases three months, before the second instillation; second, a markedly negative phase may have existed at the time of the second instillation. To this subject we will return in discussing the nature of the tuberculin reaction.

It will thus be seen that our results agree closely with those given by Wolff-Eisner, particularly in the incipient and moderately advanced cases. We have, however, obtained nothing like the high percentage obtained by the French observers. This is perhaps due in part to the fact that so large a proportion of our cases are far advanced, and that in testing the method the suspected cases and early lesions have for the greater part been used. Another reason that might be advanced is the age of our patients, 100 of whom were under 14 years old and would be likely to be frightened and cry.

Of this group the reactions were as follows:

FOURTH GROUP.

		Positive.	Negative.	Doubtful.	Per Cent. Positive.
Incipient	11	10	1	..	91
Modern advanced	16	10	6	..	62
Advanced and far advanced	17	13	4	..	70
Joints	33	19	11	3	57
Suspects	23	10	13	..	43

It is thus seen that as far as our own cases are concerned, the percentage of reactions is the same or greater among children than in cases in a corresponding stage of the disease in adult life.

In considering the value of the reaction the rational procedure seems to us to be to first consider the reaction in cases which can be proved to be tuberculous by methods other than the ocular tuberculin reaction. We have, therefore, classified as incipient only those cases in which either the

physical signs were definitely marked or the sputum was positive, putting into the class of suspected tuberculosis those cases which showed indefinite physical signs or which gave suspicious histories. Otherwise Turban's proposed classification is used throughout. With incipients our figures agree very closely with those given by Wolff-Eisner—73 per cent. as against 70 per cent. Ten patients of this class were under 14 years and the sputum was obtainable in fifteen cases, of which fourteen were positive and one negative. Of the patients whose sputa contained tubercle bacilli, five in all, three were positive, one doubtful and one negative.

In those cases moderately advanced in the stage which Turban indicates by II, our percentage of positive reaction sinks to 63 per cent., a close agreement with Wolff-Eisner's 57 per cent. Again in the advanced and far advanced the percentage is low, 64, though not nearly as low as Wolff-Eisner's, 39. A possible reason for this may be the fact that Wolff-Eisner included in his Class III only those cases *in extremis*. In any event we see—and here we are in agreement with most authors except Calmette, who seems to obtain reactions in 100 per cent. of known tuberculous cases—that a certain percentage of cases which are unquestionably tuberculous fail to react to the eye test; that this percentage grows larger as the disease progresses; and that in the latter stages many fail to react.

A discussion of the reason for this seems necessary in order that the value of the reaction as a diagnostic aid in those cases in which tuberculosis is only suspected may profitably be discussed. Unfortunately the subject is an extremely obscure one and is bound up with the cause of the tuberculin reaction in general, about which there is a vast difference of opinion and many theories. It is obvious that either some substance is present in the bodies of tuberculous subjects, not present in normal individuals, or some substance is lacking in the former which is present in the latter. According to the first hypothesis, the substance peculiar to the tuberculous reacts with the injected tuberculin, causing sufficient irritation at the point of contact to set up an inflammation; or, if the second hypothesis be correct, the substance present only in normal bodies prevents a reaction by union with an irritant substance injected. *A priori* the first of these hypotheses would seem the more reasonable, as it is known that in tuberculosis various substances are produced in the body as the result of the stimulation or irritation due to the presence of foreign bacteria. Such substances come under the classification or general head of immune bodies, bacteriolysins, opsonins, etc.

The foci of trouble, as is well known, are as a rule surrounded by

more or less well defined connective-tissue capsules with poor vascular supply, so that the intake and output of a healed tubercle is almost nil, in the case of most tubercles probably intermittent. Under these conditions the production of specific substances, as the result of the invasion either of the general circulation or of the local tissues, may be expected to be not continuous but intermittent, so that at one time there may be present in the circulation immune bodies, bacteriolysins, opsonins, etc., while at another time these bodies may be entirely absent or present in very small amount.

Now let us consider what is done when tuberculin is brought into contact with the body cells either by hypodermic injections, scarification of the skin, or conjunctival instillation. Koch's old tuberculin, as is well known, is simply a filtered extract of the dead bodies of tubercle bacilli which have been grown on glycerin bouillon. Even after filtration fragments of the bodies may be demonstrated by staining methods (Smithies, Wolff-Eisner). Therefore, the test means injecting into the body with other substances (soluble in glycerin, insoluble in alcohol) a highly complex foreign proteid consisting of cell bodies of the dead tubercle bacilli or fragments of them and their contained endotoxins.

Now, whether the true theory be Wasserman's,[6] that the tuberculin reaction consists of a chemical reaction between tuberculin and the antituberculin elaborated by the body in defense, the meeting of the two in a tuberculous focus causing a local inflammation; or Wolff-Eisner's,[1] that the reaction is caused by the action of a bacteriolysin on the bodies of the dead tubercle bacilli injected, releasing the contained endotoxin, thus causing the local inflammation which we know as a tuberculin reaction; or whether the reaction be simply that of anaphylaxis or hypersusceptibility (Vaughan and Wheeler,[7] Rosenau and Anderson[8]) in a body previously sensitized by a foreign proteid—in this case the original tubercle bacillus—the essential fact is that the tuberculous individual is sensitized by the presence of highly complex bodies which may be either present in or absent from the general circulation, or set free intermittently

According to the anatomic condition of the lesion, or what is vaguely called the patient's phase of resistance, one or other of these conditions obtains. Applying this conception practically to the consideration

6. Wasserman and Bruch: Deutsch. med. Wchnschr., 1906, xxxii, 449.

7. Vaughan and Wheeler: Tr. Nat. Assn. Study and Prevent. Tubere., 3d meeting, 1907, 237.

8. Rosenau and Anderson: Bull. No. 36, Hyg. Lab., U. S. P. H. and M.-H. S., 1907.

of healed tuberculous lesions, it may be seen that in an old focus inactive for some years and densely encapsulated, the body cells would be but slightly stimulated to react, if at all, as the specific substances have not perhaps for years been produced in response to the stimulus of invasion. Here might be expected either no reaction at all, or, if the toxin be slowly absorbed and allowed to act for a long time locally, as might occur in a cutaneous vaccination, a delayed reaction. The opposite extreme is presented in far advanced and moribund cases. Here there is no effort at anatomic encapsulation; the bacilli themselves, their toxins, and the protective substances are all present in the general circulation together. These latter, in the absence of definite proof, may be supposed to be present either (1) in small amount, due to the fact that the body can no longer respond to stimulation, or (2) in enormous excess in response to the great need of the body. In either case one would expect a negative reaction. For, in the first case the bacilli, or, according to Wasserman, the tuberculin present in the general circulation, would be seized on at that point by the bacteriolysins or antituberculin, thus failing to reach the local site of inoculation; in the second case there is such an excess of the immune body component of the bacteriolysin that, according to the theory of deflection of complement first presented by Neisser and Wechsberg,[9] the amount of available complement may be seized on by free immune body and thus none left to attach to the bacterial cell bodies injected into the conjunctiva.

Between these two extremes fall the majority of cases of tuberculosis. The most favorable, the incipient, present a class in which the lesion is yet localized and in which there is an intermittent discharge into the circulation of protective substances. These form a group in which a prompt reaction should be theoretically expected, and, in most cases, obtained. But even here not every incipient case presents the clinical appearance of good resistance, and many cases are known in which from a slight apical lesion the disease progresses steadily to a fatal termination within a few months. Here even at the start the chemistry of the blood and lymph streams may resemble that of an advanced case rather than that of a member of the class to which it seemingly belongs. Under such conditions a negative reaction would be expected, even though, clinically, the case appeared to be only incipient. This may explain the occurrence of a negative reaction in incipient cases. In other words, with Wolff-Eisner we may say "failure to react to tuberculin in known tuberculosis of an active or half-active state seems to be of grave import."

9. Neisser and Wechsberg: Studies on Immunity, Erlich, 1906, 120; München. med. Wchnschr., 1907, xlviii, 697.

It is obvious, moreover, that in any tuberculous condition there must be an ebb and flow in the resisting power and probably in the content of the blood with reference to protective substances, and that at any given time conditions might be such as to cause a negative reaction. This change in phase is well illustrated by the fact that in our second instillations six patients that were positive to a first instillation of 0.5 per cent. were later negative to 1 per cent.

As is readily seen, our actual findings fit these hypotheses. Our proportion of positive reactions is highest among the incipient cases, lowest among the far advanced. Unfortunately at the time of experimentation we did not classify the moribund and extremely far advanced cases separately from the ordinary far advanced, but our impression is that these cases were mostly negative, as was our one case of miliary tuberculosis.

Turning now to a discussion of a practical value of the reaction in cases in which tuberculosis is suspected but can not otherwise be proved, the problem rests on exactly the same footing. We should expect a failure to react under three conditions: first, if no tuberculous lesion is present; second, if the lesion is so old and inactive that the protective substances are not elaborated and the hypersusceptibility to a foreign proteid has worn off; third (and even though clinically incapable of demonstration such cases may exist) if the resistance is so low, the condition of the blood such at the time of instillation, that no local reaction follows. This latter condition is well illustrated by one of our genito-urinary patients who remained negative both to conjunctival instillation and to tuberculin injection, yet whose urine injected into a guinea-pig caused tuberculous lesion.

At this point it may be well to mention the possible objections to the technic of the speedy reinstillation of tuberculin, in that a reaction obtained under such conditions, even though the instillation be in the other eye, may be due to a hypersusceptibility caused by the first injection (Kohn[10]).

A suggestion occurs to us which we have not quite worked out, and that is the possible prognostic value of the negative reactions in incipient tuberculosis. As is well known, Wolff-Eisner considers a late positive skin reaction with an absent conjunctival reaction evidence of a healed process—that is, a focus which so slowly gives off its protective substances that only under conditions such as the skin inoculation affords, namely, a very slow absorption of the inoculated substance, will there be a reaction. With negative reactions in cases of demonstrable tuberculosis no such

10. Berl. med. Wchnschr., 1907, xliv, 1507.

favorable interpretation can be reached. "Lack of reaction capability is a serious sign."

CONCLUSIONS.

1. In apyrexial cases the test has the same value as the subcutaneous injection of tuberculin. Of our series thirteen patients were inoculated with tuberculin, the results paralleling in every case the conjunctival reaction. In pyrexia, of course, the conjunctival method is applicable where the other is not.

2. So specific a reaction as the tuberculin reaction probably indicates in all cases the presence of tuberculosis. Some authors have attributed reactions in apparently normal subjects to the association with tuberculous individuals, inhalations of tubercle dust, etc. We have had comparatively little experience with instillations in normal subjects, but to us it seems that such a specific reaction should not occur without specific cause, though this latter may be a slight focus anywhere in the body. The case most puzzling to us was that of an interne, apparently healthy, who reacted strongly. He had, however, cut his finger slightly at autopsy, and at this site there developed a small, sluggish, inflammatory area which proved later to be tuberculous.

3. The method appears to us to be particularly helpful in the cases of children whose physical signs are frequently misleading, rendering an accurate diagnosis extremely difficult.

4. In cases without symptoms which react it is perhaps safer in the present state of our knowledge to accept such a reaction simply as a danger sign and not a condition demanding active treatment, unless demanded by the clinical history.

5. A negative reaction by no means excludes a diagnosis of tuberculosis. This last conclusion seems to us perhaps the most important evidence we have to offer.

113 East Fifty-sixth Street—125 East Seventy-first Street.

PARASITES FOUND IN NEW YORK CITY.*

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This paper is written as an indication that in many ways New York is a center for the observation of tropical diseases, and in an effort to awaken a realization of the conditions obtaining in certain parts of the community. An occasional case of leprosy occurs in New York; beriberi, pernicious malarial fevers and other maladies, the early symptoms of which are not sufficiently severe to prevent the infected individuals leaving tropical countries, are not infrequent. Since the emigration of large numbers of people from northeastern Europe, since the intimate relations with the Philippines and Porto Rico subsequent to the Spanish War, and especially since the great influx of West Indians, individuals who are the hosts of a variety of most interesting intestinal and blood parasites have appeared at various dispensaries in New York.

It is a difficult matter to examine all patients that apply for treatment. By far the majority of the patients have no symptoms referable to intestinal parasites and come for other complaints. Many of them, when directed to bring a stool, treat the request as a joke or think some hoax is being perpetrated at their expense. The only way to get specimens from many of them is to give an enema on the occasion of their first visit. In the clinic of the department of Applied Therapeutics, Vanderbilt Clinic, there have been a good number of patients who showed eosinophilia who failed to return with the requested specimen.

SPECIES OF PARASITES ENCOUNTERED.

1. *Tænia saginata.*—This parasite is so frequently encountered and its symptoms are so insignificant that it deserves no special mention.

2. *Tænia solium.*—This may be dismissed as a parasite so rare as to be almost unheard of. Several years ago I visited some of the "tapeworm experts" in an effort to find a specimen of *T. solium,* with negative results. It is possible that these parasites are not recognized, and it is also possible that they have been found and allowed to go unrecorded—a too common occurrence in the practice of the busy physician.

3. *Tænia nana.*—The following case has already been reported to

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the Practitioners' Society by the head of the department, Dr. Samuel W. Lambert:

Old Series 6125.—*Patient.*—J. W., German. Complaint, stomach trouble and cough. Admitted Sept. 20, 1906. October 5: Stool, *Tænia nana*, ova and parasites.

Wood[1] says:

The eggs of the tapeworm (*T. nana*) are presumed to be spread by the infection of food by the excrement of mice and rats; (and by) secondary infections taking place from person to person, as seems probable from the report of Ransom,[2] where 38 out of 106 persons were inmates of public institutions.

Ransom's report covers all cases occurring in man up to September, 1904. Stiles[3] says:

The geographical distribution of all positive and probable cases known for this country is: Philadelphia, 1 case (Spooner); Washington, D. C., 12 cases (Murray, Garrison, Hemler, Olesen); Charleston, S. C., 1 case (Stiles); Macon, Ga., 3 cases (Stiles); Jackson, Miss., several cases (De Velling); Galveston, Texas, 1 case (Moore); Amarillo, Texas, 4 cases (Magnenat).

4. *Dibothriocephalus latus.* — Indigenous to Europe, Turkestan, Japan and South Africa (Wood), the *Dibothriocephalus* has been imported into this country. A diagnosis of its proglottides is easy, by their great relative breadth and the rosette-shaped uterus opening on the center of each segment. The demonstration of the ova is fairly easy, by exerting pressure on a coverslip lying over an ovum and observing the membrane at the opercular end of the egg rupture.

The dibothriocephalus anemia has attracted attention for a number of years. Talquist[4] has recently been able to separate from the decomposing proglottides a lipoid substance which produces in animals marked anemia and lymphocytosis. It is said to be similar to the lipoid elaborated in certain parts of the intestinal tract, and Talquist suggests that an overproduction of the intestinal lipoid is the possible cause of primary pernicious anemia, and that the lipoid material of carcinoma is responsible for the anemia and cachexia. Wood,[5] on the other hand, says:

It is certain, however, that only a few persons carrying these worms suffer from severe types of anemia, and it is probable that some congenital or acquired deficiency exists in the blood-making organs in those cases with fatal anemia.

In this department of the Vanderbilt Clinic two patients, mother and daughter, were the hosts of this parasite. These were both imported

1. Wood: Chemical and Microscopical Diagnosis, p. 352.
2. Ransom: Bull. 18, Hyg. Lab., U. S. P. H. and M.-H. S., Washington, D. C.
3. Stiles: New York Med. Jour., 1903, lxxviii, 877.
4. Talquist: Ztschr. f. klin. Med., 1907, lxv, 427-532.
5. Wood: Chemical and Microscopical Diagnosis, 148.

cases. Neither patient was anemic, and from both perfectly preserved specimens of the worm were removed. The evidence, then, appears to indicate that the *Dibothriocephalus* must decompose inside the body in order to produce anemia.

An intensely interesting point in this connection is the fact that Nickerson[6] has reported a case of infection with *Dibothriocephalus latus* originating in the United States. The patient was born in Ely, Minnesota, April 25, 1902. The father, three years after coming from Finland, passed a *Dibothriocephalus latus*. On August 8, 1904, the patient passed a similar worm, the scolex being secured. The child had often eaten of fish caught in the lakes about Ely, and of salt fish probably from the great lakes, but never any imported fish. Nickerson states that he is informed by dealers that all fish imported and eaten by Scandinavians are salt-water fish. He has found the larvæ of the *Dibothriocephalus* in fish from the great lakes, but without feeding experiments he could not determine the species. He could find no reports from this country of infection of dogs, cats or foxes, the other animals capable of becoming the definitive host of this parasite, and concludes that there has been a local infection of the lakes about Ely.

Nickerson's case introduces questions of grave sanitary and economic import which should engage the interest of medical bodies in the districts involved. In view of the grave and sometimes fatal anemia produced by *Dibothriocephalus latus,* it seems just as legitimate to secure and enforce regulations directed against the spread of infection by this parasite as it is to legislate against the habit of indiscriminate spitting or to quarantine against contagious disease. It is true that the disinfection of stools would be difficult to enforce, but physicians could be required to report cases and local health boards could give patients directions as to the disposal of feces.

5. *Uncinaria Americana.*—Among the parasites found in New York perhaps the most important is *Uncinaria Americana,* or hookworm. It is astonishing to realize how few people appreciate that there is a substantial West Indian population in the city, and that many of these West Indians are the subjects of hookworm infection. These parasites differ morphologically but little from the old-world species, and may give evidence of their presence by eosinophilia and secondary anemia. The ova or parasites may be found in the stools.

Case 1 (Old Series 6702).—Dec. 24, 1906. *Patient.*—West Indian; complaint, sore throat and cough. Blood examination: Eosinophiles, 48.5 per cent. Stool:

6. Nickerson: Jour. Am. Med. Assn., 1906, xlvi, 711-713.

Ova of *Uncinaria, Trichocephalus dispar* and *Ascaris lumbricoides.* Second blood examination: Eosinophiles, 52 per cent.

Case 2 (Old Series 7292).—March 4, 1907. *Patient.*—West Indian. Complaint, constipation. Eosinophiles, 8 per cent. Stool: Numerous ova of *Uncinaria* and a few of *Trichocephalus dispar.*.

Case 3 (New Series 13031).—Nov. 29, 1907. *Patient.*—West Indian; applied for treatment for syphilis. Eosinophiles, 5.5 per cent. Stool: Ova of *Uncinaria* and *Trichocephalus dispar.*

Case 4 (New Series 16912).—Jan. 3, 1908. *Patient.*—Peruvian. Symptoms of hyperacidity. Eosinophiles, 14 per cent. Stool: Numerous ova of *Uncinaria.*

Case 5 (Old Series 3766).—Dec. 8, 1905. *Patient.*—German. Complaint, appendicitis. Patient has been in Egypt within three years. Eosinophiles, 19 per cent. Stool: Ovum found, probably of old-world worm, identified only as uncinaria.

Occasion is taken to record two other cases the histories of which can not be found. One was an instance of infection with *Uncinaria* and *Trichocephalus dispar,* the host being a West Indian; the other was a Porto Rican whose stools showed also the embryos of *Strongyloides intestinalis.*

The present opportunity is also taken to record three cases, occurring in West Indians, found at the Hudson Street Hospital; two of infection with *Uncinaria* and *Trichocephalus,* and one with *Uncinaria Trichocephalus* and *Ascaris lumbricoides.*

In these cases it is interesting to note:

1. None of them gave symptoms that could be directly referred to the presence of the parasites, and although hemoglobin estimations were not made, the blood smears did not show the appearance of secondary anemia.

2. Only one case was unassociated with other parasites.

3. Some of the patients had been away from the source of infection for as long as three years.

4. The eosinophilia varied from 5.5 to 52 per cent.

5. Absence of eosinophilia and prolonged removal from the source of infection do not exclude the possibility of uncinariasis.

The interest concerning uncinariasis in this country is largely attributable to the valuable work of Stiles,[7] the describer of the American variety, and efforts of the Porto Rico Anemia Commission.[8] Their reports show that about 90 per cent. of the agricultural and 50 per cent. of the urban inhabitants of Porto Rico harbor this parasite. Stiles' trip to the southern states has revealed the great prevalence of the disease in the United States. Claytor[9] in 1902 reported a case from Westmore-

7. Stiles: Bull. 10, Hyg. Laboratory U. S. P. H. and M-H. S.

8. Rep. Porto Rico Anemia Commission: Anemia in Porto Rico, 1904, and 1906-'07.

9. Claytor: Am. Jour. Med. Sc., 1902, cxxiii, 28.

land County, Virginia. Dunbar[10] has found one Texas case. Smith[11] found in eighty-six students of the University of Texas eight cases, all the patients being natives of the state, whose homes were distributed over a wide area. From the same state Moeller[12] reported one case, and W. D. Jones,[13] himself a victim of the disease, reported three. Toole[14] has reported a case in a native Georgian, the *Uncinaria* being associated with *Amœba dysenteriæ* and *Trichomonas intestinalis*. This patient had been in Alabama a few months before applying for treatment. Bass[15] has shown that the infection is prevalent in Mississippi. Nicholson[16] has reported ninety cases from Onslow, Jones, Lenoir, Craven, Pender and Duplin Counties, North Carolina. From the same state Rankin[17] was able to collect reports of 147 cases, and Dr. Alice E. Johnson[18] has published a report of one. Claude Smith[19] has reported three cases from Georgia, one of which may have originated in Florida, and states that he does not doubt that every county of the former state is infected. Warfield[20] has recorded five Georgian cases from about Savannah, and in an examination of sixty boys in the Bethesda Home for Boys, seven miles from Savannah, he found forty-eight to be infected.[21] Homan[22] reports a case from Missouri which probably developed in Alabama, while Betts[23] has observed nine or more cases in Conecuh County, Alabama. Mason[24] has reported fifteen cases from the Birmingham district, and mentions Bondurant's contribution[25] of reports of fifty cases in and around Mobile County, and Skinner[26] reports five cases from Selma. Adams[27] reports a case from Washington, D. C., infected in St. Mary's County, Maryland. Williamson,[28] in 150 consecutive stool examina-

10. Dunbar: Texas Med. News, 1905, xiv, 3.
11. Smith: Am. Jour. Med. Sc., 1903, cxxvi, 768.
12. Moeller: Texas Med. News, 1904, xiii, 148.
13. Jones: Med. Recorder, Shreveport, La., 1904, i, 554.
14. Toole: Alabama Med. Jour., 1905-'06, xviii, 9-12.
15. Bass: Jour. Am. Med. Assn., 1906, xlvii, 185.
16. Nicholson: Charlotte Med. Jour., 1904, xxv, 376.
17. Rankin: Charlotte Med. Jour., 1904, xxv, 380.
18. Johnson: Carolina Med. Jour., 1905, liii, 792.
19. Claude Smith: Charlotte Med. Jour., 1904, xxv, 320.
20. Warfield: Med. Rec., 1904, lxvi, 9.
21. Warfield: Am. Med., 1904, lxvi, 9.
21. Warfield: Am. Med., 1904, vii, 60.
22. Homan: Jour. Missouri Med. Assn., 1905, ii, 764.
23. Betts: Mobile Med. and Surg. Jour., 1906, ix, 87.
24. Mason: Alabama Med. Jour., 1904-'05, xvii, 20.
25. Bondurant: Tr. Med. Assn. Alabama, 1903, 293-299.
26. Skinner: Mobile Med. and Surg. Jour., 1903, iv, 37.
27. Adams: Arch. Pediat., 1906, xxiii, 241.
28. Williamson: Jour. Am. Med. Assn., 1905, xlv, 1955.

tions in the Canal Zone, found, among other parasites, *Uncinaria* forty-six times, *Trichocephalus* forty-eight times, *Ascaris lumbricoides* twenty-five times, *Amœba dysenteriæ* twenty-one times, and *Strongyloides* ten times.

Stiles[29] says that since his description of the American hookworm in 1902 Loos has shown that "earlier observers had specimens of this worm mixed in with their material of *Anchylostoma duodenale*, but that they had failed to recognize that they were dealing with more than one form." Writing in September, 1906, he says that he has recently received specimens from China and the island of Guam.

While it is not intended to make a complete review of the literature of the subject, it is hoped this short allusion to the geographical distribution of uncinariasis in the United States will be an aid in diagnosis by helping clinicians to suspect the disease.

With our considerable West Indian population, which will probably in time invade territory unprovided with drainage emptying into sea water, and with workmen returning from the Canal Zone, it is a question whether cases will not develop in the neighborhood of the city, if they have not already developed. In view of the grave symptoms to which uncinariasis may give rise, it is not altogether irrational to consider the advisability of regulation of these cases by sanitary boards or report of them to the proper authorities.

6. *Strongyloides stercoralis.*—Two cases of this parasite have been found; in one of the patients, whose history can not be found, the condition was associated with uncinariasis, and the infection probably occurred in Porto Rico.

A short detail of the second case follows:

New Series 11863.—*Patient.*—D. S., native of Antigua, Nov. 19, 1907. Symptoms of marked loss of compensation due to mitral stenosis or adherent pericardium. Blood: Red cells, 4,800,000; white cells, 14,000; hemoglobin, 85 per cent.; eosinophiles, 21 per cent. Stool: Embryos of *Strongyloides*, and ova of *Bilharzia*, lateral-spined.

7. *Bilharzia.*—The following cases illustrate *Schistosomiasis*, or infection with *Bilharzia:*

Case 1.—Old Series 5074.—Patient.—G. R., admitted Aug. 1, 1906. Complaint, pain in back and in penis on urinating. Went to South Africa in 1899, and was in Boer war. Was perfectly well until 1902, when he went to Hong Kong, where symptoms began. Blood: Eosinophiles, 12 per cent. Urine: Terminal-spined ova of *Bilharzia hæmatobia.*

Case 2.—New Series 11863.—Patient, D. S., native of Antigua. (For details see same case.)

29. Stiles: Johns Hopkins Hosp. Bull., 1902, xvii, 313.

Gunn[30] has reported two cases of intestinal infection in Porto Ricans living in San Francisco, and as his cases were the first two reported in the United States the present makes the third. In both of Gunn's cases the ova were lateral-spined; both were associated with *Uncinaria* and *Trichocephalus dispar,* and one with *Strongyloides.* He has been able to find only six cases reported in the United States. He can not accept two of these—that of Booth, reported in 1882, and that of Walker,[31] both of which were supposed to have originated in Illinois. Holcomb[32] also discredits these two alleged domestic cases, and is not convinced of a case reported by Lewis[33] in 1900. B. F. Curtis[34] in 1895, Brooks[35] in 1897, Pool[36] in 1903, O'Neill[37] in 1904, and Robbins[38] in 1907, have each reported a case, all of which were imported and involved the bladder.

In 1902 Manson[39] reported a case of intestinal infection in a young man who had lived many years in the West Indies, his symptoms starting in Antigua, the island from which the present case came. The ova presented lateral spines. When in San Francisco Manson examined the ova from Gunn's patients and said that they corresponded to those of his West Indian case. He expressed himself to Gunn at that time as believing that the lateral-spined and terminal-spined ova were produced by different species. Gunn feels that Catto's[40] discovery in Japan of a new worm similar to *Bilharzia hæmatobia,* but with readily distinguished eggs, "lends color" to Manson's belief. In his book, "Tropical Diseases,[41] Manson says:

> Strange to say, in ova found in the bowel, the spine is generally placed laterally; whereas in ova coming from the walls of the bladder the spine is invariably terminal. In the ova in the feces of the West Indian case I have already alluded to, the spine was placed laterally and directed backwards; in this case there was no hematuria, nor were there ova in the urine. This lateral situation has been explained in various ways, one suggestion being that it is a consequence of the compression exercised by the muscular coat of the intestine on the parent worm while the ova are passing the shell glands; the relations of certain of the reproductive organs of the worm are supposed to be altered by this compression. Possibly there are two species of *Bilharzia,* one with lateral-spined ova, depositing its eggs in the rectum only, the other haunting bladder or rectum indifferently.

30. Gunn: Jour. Am. Med. Assn., 1906, xlvi, 1031.
31. Walker: Jour. Am. Med. Assn., 1900, xxxiv, 390.
32. Holcomb: U. S. Nav. Med. Bull., 1907, i, 55-80.
33. Lewis: New York Med. Jour., 1900, lxxi, 1057.
34. Curtis: Ann. Surg., 1896, xxiii, 56.
35. Brooks: Med. Rec., 1897, li, 492.
36. Pool: Proc. New York Path. Soc., 1903, new series iii, 83.
37. O'Neill: Boston Med. and Surg. Jour., 1904, cli, 453.
38. Robbins: Am. Jour. Urol., 1907, iii, 40.
39. Manson: Brit. Med. Jour., 1902, ii, 1894.
40. Catto: Jour. Trop. Med., 1905, viii, 70. Katsurada: Jour. Trop. Med., 1905, viii, 108.
41. Manson: Tropical Diseases, 3d ed., 1903, 613.

Holcomb[42] recognizes two species: *Schistosoma hæmatobium*, the eggs of which have a terminal spine and occur in the urine; and *Schistosoma mansoni*, the ova having lateral spines and being voided in the feces. The article here referred to is very complete and furnishes an excellent bibliography on schistosomiasis in general.

Perhaps a word as to the new-world distribution of this disease would not be malapropos.

Lahille[42] has reported three cases of intestinal schistosomiasis from Martinique. Holcomb[43] states that the Porto Rico Anemia Commission found twenty-one cases in combination with uncinariasis in a series of 1,822, and that he knows of 167 Porto Rican cases. In his later article[43] he details in full nine intestinal cases.

In Williamson's report of 150 consecutive examinations in the Canal Zone, previously alluded to, no reference is made to *Schistosoma*.

8. *Filaria sanguinis hominis*.—The following report gives examinations of blood and urine in a case of infection with filaria:

Old Series 6765.—*Patient*.—D. P., native of Barbadoes. Dec. 27, 1906. Complaint, sediment and milky appearance of urine. Blood: No eosinophilia in a count of 200 leucocytes. Urine: Chylous with blood cltos showing esveral actively motile filaria embryos. December 31. Stools: No ova. Urine: As on December 27.

Jan. 6, 1907. Blood examined at midnight: Many filaria embryos, maximum, six in one field, (low power). ?

January 7. Blood: Hemoglobin, 100 per cent. (Fleischl); white cells, 5,100; red cells, 4,800,000. Differential count (200 cells): Poly. neut., 56 per cent.; large lymph., 6.5 per cent.; small lymph., 26.5 per cent.; eosinophile, 9.5 per cent.; basophile, 11.5 per cent.

9. *Trichomonas intestinalis*.—I have encountered one case of infection with this parasite at the Hudson Street Hospital. The source of the infection was one of the southern states and the blood showed an eosinophilia of 35 per cent. Repeated examinations failed to reveal evidence of associated parasites.

The cases here reported occurred in busy dispensary practice, with no special effort directed toward finding them. It is probable that many have been overlooked and that a systematic investigation would give rise to startling revelations.

TREATMENT AND PROPHYLAXIS.

The therapeutic measures indicated in cases of tapeworm are too well understood to warrant consideration at present. Clinicians are so familiar at the present day with the relation between intestinal parasites

42. Lahille: Ann. d'hyg. et de méd. colon., 1906, ix, 262.
43. Holcomb: Mil. Surg., 1907, xx, 459-467.

and morbid conditions of the blood that the time-honored warning, "in all cases of anemia always examine the stools, etc.," may be dispensed with. In dibothriocephalus anemia the principal step toward recovery is taken when the parasite has been expelled. Aspidium still seems to give the best results. In the case of infection with *Tænia nana* mentioned here, the parasites were obtained by the use of that drug.

In the management of uncinariasis, thymol is the drug which has gained the best reputation by its universally good results. The one point to be borne in mind in its use is that its absorption is increased in the presence of alcohol and oil and its toxic action thereby magnified. Reference is made to the work of Stiles[7] for details of experiments on toxicity of thymol. Our practice at the clinic is to give ten to thirty grains at night with a saline in the morning, avoiding the use of castor oil.

The drug treatment of bilharziasis is very discouraging. A certain number of the afflicted, when removed from the danger of constant reinfection, show an amelioration of the symptoms and a tendency to outgrow the disease. Surgically the treatment of the disease has acquired a significance that is surprising to the physicians of the western hemisphere. Madden[44] in his excellent book devotes considerable attention to the subject; it is well worth reading.

In this connection it is interesting to note that Crimp[45] has drawn attention to the not infrequent involvement of the vermiform appendix, and Burfield[46] has recently reported such a case.

Thorough cooking of fresh-water fish and disinfection of infected stools are the necessary prophylactic measures against infection with *Dibothriocephalus latus.*

In uncinariasis and bilharziasis, as the embryos invade the human organism through the skin, the habit of going barefoot should be discouraged in the districts in which the diseases prevail. All dejecta containing ova should be destroyed.

149 East Sixty-second Street.

44. Madden: Bilharziosis, New York, William Wood & Co., pp. 51, 57, 67, 70, 74, 76, 77.

45. Crimp: Jour. Trop. Med., 1905, viii, 67.

46. Burfield: Lancet, 1906, i, 368.

MULTIPLE EPENDYMAL GLIOMA;

ONE TUMOR OF THE FOURTH VENTRICLE, THE OTHER OF THE FRONTAL LOBES.*

PETER BASSOE, M.D.
CHICAGO.

REPORT OF A CASE.

Patient.—An army officer, 50 years old, unmarried, was under my care during the last two weeks of his life. For much of the previous history I am indebted to Dr. A. Howard Smith, of Marietta, Ohio.

History.—Both parents died of heart disease. The patient had spent most of his life at army posts in the west. He is said to have been a neat, sober, quiet, well-balanced man. There is a probable history of syphilitic infection twenty-five years ago. About ten years ago he was operated on for fistula in ano. He had considerable purulent discharge from the ears and had a mastoid operation many years ago. Ten years ago he was retired from active service. During the last two and a half years he served as a recruiting officer. Inquiry at the Adjutant General's office in Washington brought the following list of ailments for which he was treated between 1878 and 1897, presumably in chronologic order, though there is no statement to that effect: acute rheumatism, tertian intermittent fever, catarrh, mumps, acute muscular rheumatism of the neck, abscess of right buttock, complication, fistula in ano, acute diarrhea, dry catarrh of middle ear, right side; suppurating glands of neck, left side; subacute synovitis of right wrist, chronic suppurative inflammation of left middle ear, suppurative ganglion of right wrist, ganglion of right wrist and necrosis of lower end of radius, ischiorectal abscess, fistula in ano, blind externally. From Sept. 1, 1906, to Oct. 23, 1907, he was treated for inflammation of the nose, pruritus ani, disease of the ear and inflammation of the middle ear.

Last Illness.—During the last eight months of his life he gradually grew forgetful both as regards his duties and his personal affairs. Naturally orderly, punctual and scrupulously tidy, he now would forget appointments, wear his uniform at unusual times and show other minor lapses. Nothing serious occurred, however, until about seven weeks before his death. On Feb. 25, 1908, he obtained a few days' leave of absence to visit another city. He forgot his satchel and money, changed hotel three times, wrote incoherent letters, came back March 3, several days late, untidy in appearance and confused mentally, and seemed to have forgotten his duties entirely. After this time he never spoke of his work. On that day, March 3, he was seen by Dr. Smith, who informs me that there was no elevation of temperature. The urine was free from albumin and contained hyaline casts. From March 10 on the patient would void urine in his clothes, occasionally also the feces. There was no dribbling or retention of urine. These accidents made no impression on him and were probably due to his mental state. He showed no emotion, but recognized people about him. His sleep was irregular; he would sleep all night on fifteen grains of trional. He did not complain of headache or other pain. Sometimes he would sit for hours and tap on his chair. He was always good-natured and tractable, never resistive. Thorough examina-

* Read before the Chicago Neurological Society, May 29, 1908.

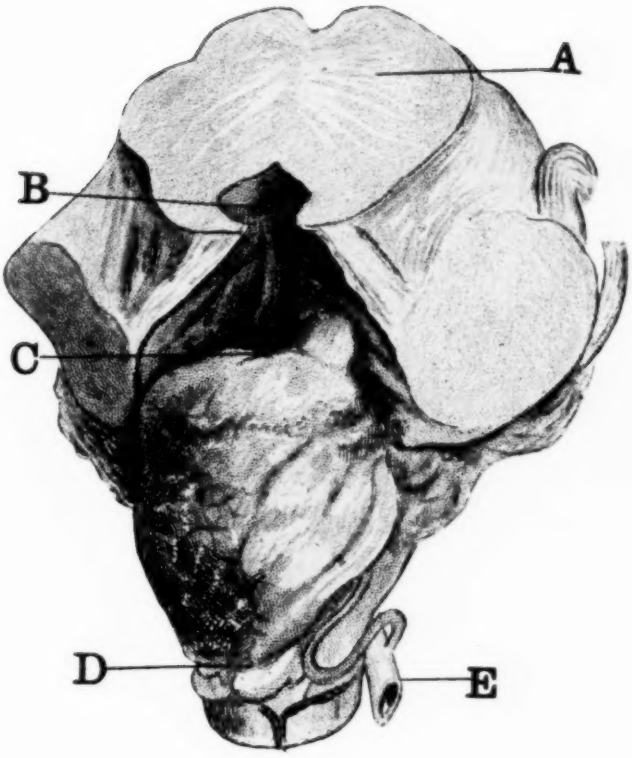

Fig. 1.—Tumor of the fourth ventricle: a, cut surface of pons; b, aqueduct of Sylvius; c, upper border of tumor; d, lower border of same; e, right vertebral artery. The picture does not properly represent the prominence of the tumor posteriorly.

tion of the eyes and accessory sinuses was negative, and no fresh disease of the ears was found. Three or four times the patient vomited in the morning. There wsa no change in his mental condition in the three weeks preceding his admittance to the Presbyterian Hospital on March 29, when he came under my care. He had been perfectly quiet and tractable on the twelve hours' journey to Chicago and only caused trouble to his companions by soiling his compartment during the night. He walked into the hospital.

Examination.—This was made March 29, two weeks before the patient's death. The patient was a well-built and well-nourished man weighing 167 pounds. He was quiet and composed mentally, very good-natured, perfectly serene and satisfied. He was disoriented both as to time and place; thought that he was at Wheeling, West Virginia. He knew his sister and brother-in-law and called them by name. Otherwise he seemed to have no grasp on his surroundings. Asked about his previous life, he gave the year of his graduation from West Point correctly, but could give no account of his doings during the last twenty-five years. His answers were brief and as a rule not prompt. He was very docile and cooperated well in the examination. The pupils were equal and reacted normally. The ocular movements were normal. There was a slight but distinct bilateral optic neuritis. Vision was apparently fairly good; it could not be accurately measured on account of the patient's mental condition. The hearing was impaired, more so in the right ear. Both facial nerves were intact. The knee-jerks and ankle-jerks were increased, but there was no clonus. There was no Babinski sign. The cremaster reflex was present on the right side, absent on the left side. The abdominal reflex was uncertain. The wrist-jerks and elbow-jerks were normal. There was no paralysis, no incoordination and no speech disturbance. Sensation was apparently intact. The heart was enlarged to the left, the pulse full, of high tension, the peripheral arteries sclerotic. The blood pressure measured with a Stanton apparatus equaled 185 mm. of mercury. There were cutaneous scars in various parts of the body and depressed scars in the frontal bone and at the lower end of the right radius. The urine was normal. The temperature was normal; the pulse varied from 56 to 64, always regular. On March 30 the blood count was, reds 5,280,000, whites 15,800. The temperature ranged from 98.4 to 99, the pulse from 64 to 88.

Clinical Course.—The patient was placed on mercurial inunctions, as cerebral syphilis was considered the most plausible diagnosis.

March 31 the patient vomited while eating breakfast. The blood pressure was 170. At 9 p. m. lumbar puncture was performed. Clear fluid under apparently normal pressure was obtained and 6 c.c. were removed. The fluid contained much albumin, as a ring one-fourth inch thick was produced on making the nitric acid contact test. After centrifuging for one hour a small number of small, round, mononuclear cells was found in the sediment. There was no change in pulse or respiration or otherwise during or after the puncture.

April 1: The patient vomited in the afternoon. The temperature reached 99.8, the pulse ranged from 80 to 92.

April 2: The patient slept poorly and vomited after breakfast. In the afternoon he gradually lapsed into coma with very deep respiration. The blood pressure was 210. After withdrawal of 300 c.c. of blood at 3:45 p. m. the pressure was 215. At 5 p. m. 425 c.c. additional were removed and the pressure lowered to 195. At 10:30 p. m. the pressure was 180.

April 3: The patient rested well during the night and was fairly bright in the morning. The blood pressure was 170. The temperature at noon was 100.4, at 8 p. m. 97.8. Hemoglobin was 90 per cent.; leucocytes, 15,500.

April 4: The pressure was 190. In the afternoon headache seemed to be present.

April 5: In the afternoon the patient again lapsed into coma, with temperature 100.1 and signs of consolidation of the lower lobe of the left lung. The pressure at 11 a. m. was 185, at 4 p. m. 200. At 10:30 p. m. 650 c.c. of blood were withdrawn and the pressure fell to 145.

April 6: The temperature reached 104.4, but the patient was brighter. The pressure was 150. During the next few days the patient was quite bright, the lung gradually cleared up and the temperature declined to 99.4 on the 9th. The blood pressure gradually rose to 170 on the 10th. On the 7th the leucocyte count was 20,600.

April 11: Optic neuritis was present as before. The patient's general condition was worse toward evening. The temperature was 101.4, blood pressure 190. The lungs again showed signs of consolidation and the patient was rapidly failing.

April 12: At 9 a. m. the pressure was 180. The patient was restless during the night and unable to take nourishment. At 2 p. m. the pressure was 151, pulse 112 and strong; respirations, 28 and irregular. Chill lasting fifteen minutes commenced at 2:45. The patient died at 3:30 from failure of respiration, while the pulse remained strong and regular to the end.

AUTOPSY FINDINGS.

General Appearance.—The autopsy was held by me four hours after the patient's death. The body was well nourished. There was no change in the large serous cavities and their lining. Both lungs were edematous and there was hypostatic bronchopneumonia of both lower lobes, more marked on the left side.

Heart and Aorta: The wall of the left ventricle of the heart was greatly thickened; otherwise the heart showed no change. The circumference of the aortic opening was 9 cm. The ascending portion of the arch of the aorta was the seat of an aneurismal dilatation, from the upper end of which the innominate artery was given off. The greatest circumference was 11 cm. and the sac was lined by thick, largely calcareous sclerotic patches. The transverse portion of the arch was the seat of large, raised, only slightly calcareous patches, while only a few small ones were seen in the descending portion.

Alimentary Tract: There was no change in the alimentary tract except moderate atrophy of the mucosa of the stomach. There was passive hyperemia of the liver, spleen and kidneys.

Cranium: On examination of the skull the depression in the frontal bone noted clinically was found to involve the outer plate only. The dura showed no change. The brain was heavy, weighing 1,680 gm. The gyri were broad and flattened. There was almost no subdural fluid. On palpation the left frontal lobe was distinctly soft.

Examination of the Brain.—After hardening in 4 per cent. formaldehyd, frontal sections were made. They revealed the presence of a large tumor occupying the frontal portion of the cerebrum on both sides, extending from one hemisphere to the other across the median line, as seen in Figures 2 and 3.

Left Hemisphere: Tumor tissue was seen in the white substance 1 cm. behind the frontal pole, and on passing backward the tumor rapidly increased in width so that on a section 3.5 cm. behind the frontal pole there was a central tumor area measuring 6 cm. from side to side and 5 cm. from above downward. In this section it did not touch the gray substance at any point.

Right Hemisphere: In the corresponding section on the right side only a nodule 3 cm. in diameter, close to the cortex above, was found. A section 2 cm. farther back and passing through the anterior part of the corpus callosum is pictured in Figure 2. Here large areas of hemorrhage and softening were seen. The clot in the right frontal lobe measured 2.5 by 1.5 cm.

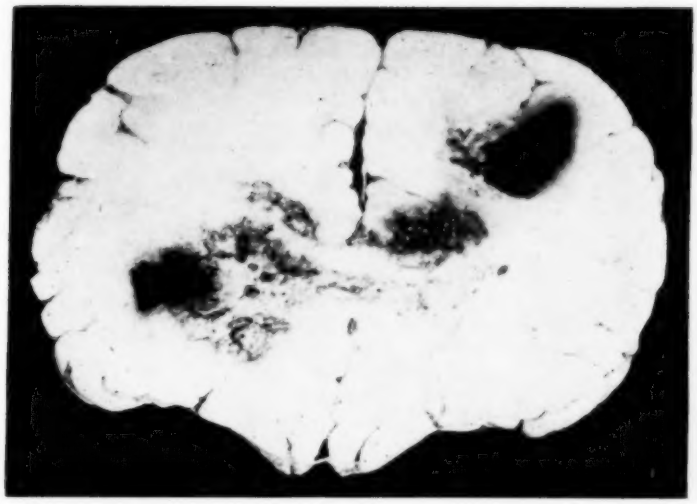

Fig. 2.—Frontal section of cerebrum through anterior end of corpus callosum, looking forward. Two large hemorrhages and large degenerated tumor areas are seen.

Fig. 3.—Frontal section through anterior commissure and tips of the temporal lobes, looking forward. A large hemorrhage on the left side is seen.

Figure 3 represents a section through the anterior commissure and tips of the temporal lobe. The anterior portion of both lateral ventricles was seen to be filled with partly necrotic tumor tissue, and the adjacent white substance and the basal ganglia on the left side were infiltrated with tumor. A clot measuring 2.5 by 1.8 cm. was seen in the left external capsule. The tumor only extended 1 cm. behind this section. Here the rounded free end of the intraventricular growth was seen in the left lateral ventricle and the posterior end of the clot in the left external capsule was also seen on this section.

Other Changes: Behind this level no tumor tissue was found in the cerebrum and no other alteration except a moderate enlargement of the ventricles and numerous lacunæ in the basal ganglia. The vertebral, basilar and cerebral arteries were rigid, thickened, in places dilated and presented extensive sclerotic, but not calcareous, patches.

Examination of Fourth Ventricle Tumor.—A growth was seen to project between the bulb and under surface of the cerebellum. The latter was only loosely adherent to the growth and could readily be separated. Its inferior surface was raised and indented, much more so on the right side.

This tumor measured 3.4 cm. in length, 2.5 cm. in width and 2.5 cm. from above downward. Its outer surface was lobulated and covered by a thin, fibrous membrane. It was firmly attached to the ependyma for a distance of 2.5 cm. The upper end of the attached portion on the right side was above the level of the striæ medullares, on the left side 7 mm. lower. The lower end was a little below the calamus scriptorius. Above it was adherent to the cerebellum, the under surface of which was indented. The ependyma was dark brownish-gray, thick and finely granular also in the part attached to the cerebellum. When a section was made through the middle of the attached portion of the tumor the latter was found to be firmly attached across the entire upper surface of the bulb, no free cavity remaining between them. The foramen of Magendie was covered by the adherent posterior pole of the tumor. The cut surface of the tumor was grayish-white and appeared to be very vascular. Several large vessels were seen to pass into it.

HISTOLOGIC EXAMINATION.

The Tumor in the Fourth Ventricle.—The most striking feature in the microscopic picture was the great number of blood vessels, most of which were thick-walled and generally surrounded by layers of radially placed tall cells separated from the vessels by a mass of largely radial thin fibers, undoubtedly glia fibers, though Weigert's glia stain was only partly successful. In places round, nucleated tumor cells filled with blood pigment were seen in large numbers near the blood vessels. In many places the walls of the latter were thick, hyaline and degenerate. Most of the tumor cells were small, round or oblong, and possessed little cytoplasm. Large astrocytes were not seen. No mitotic figures were seen. The border between the tumor and the bulb, which was distinct to the naked eye, in most places was also sharp under the microscope, except near the median line and for a short distance to the left of it, where one passed from bulbar nuclei to tumor tissue without any well-defined intervening fibrous or ependymal layer. On this diffuse border was seen a small duct-like structure lined by tall cylindrical cells and containing a small cluster of cells adhering to each other. It was the only structure of its kind encountered in any of the sections.

The Frontal Lobe Tumor.—This was also chiefly made up of small, nucleated, mostly round, cells with little cytoplasm. The abundance of vessels was even more striking than in the fourth ventricle growth and here the vessels were mostly thin-walled, wide, and in places so thickly set as to give an appearance

of angioma. Well-preserved tumor tissue was only seen in islands, on account of extensive necrosis and hemorrhage. This tumor differed from that in the fourth ventricle chiefly by its thinner, more dilated vessels and the more extensive necrotic and hemorrhagic areas. There was a gradual transition between the tumor and brain tissue. In sections made from the right side the tumor tissue was less degenerated; otherwise the structure was similar.

Bulb and Upper Cervical Cord.—Weigert-Pal specimens of the bulb and upper cervical cord failed to show any degeneration.

Basilar Artery.—Sections of the dilated basilar artery showed marked and uneven intimal thickening with calcareous deposits and vacuole formation in the thickened intima. A few collections of small mononuclear round cells were seen in the adventitia.

Lung.—There were bronchopneumonic areas, with extensive hemorrhage into the alveoli and considerable edema.

Wall of Left Ventricle.—With the exception of slight increase in interstitial fibrous tissue there was no change.

Aorta.—There was marked, uneven thickening of the intima in which there were large hyaline, degenerated areas with many vacuoles and cholesterin slits and heaps of lime salts. In the media, accumulations of small, mononuclear cells, surrounding thin-walled, engorged vessels, were seen.

Spleen, Liver and Kidney.—There was marked sclerosis of vessels and marked passive hyperemia. The Malpighian bodies were well preserved. The liver presented passive hyperemia and moderate fatty change. The kidney was little changed aside from passive hyperemia. A few fibroid glomeruli were seen.

OCCURRENCE OF MULTIPLE GLIOMA.

The unique feature of this case is the presence of two large tumors at opposite ends of the brain, each having the structure and appearance of primary ependymal glioma. The frontal tumor appeared to have originated from the ependyma of the lateral ventricles and in places was so vascular as to deserve the name "angio-glioma." It was the seat of large hemorrhages. The second tumor, located in the fourth ventricle, also had the appearance of ependymal glioma. Each tumor had the characteristics of primary glioma, but the possibility of one being an implantation growth can not be absolutely denied, though it is most improbable. The unusual features of the present case are apparent in view of the following quotation from Borst:[1] "Multiple occurrence of glioma has not been observed with certainty, at least so far as genuine tumor-like proliferation of the glia is concerned." L. Bruns[2] says: "In the central nervous system glioma is usually solitary, though occasionally near a large growth one or two small nodules are seen which are separated from the large one, but probably we are here dealing with regional metastases. At great distances, even in the central nervous system, gliomata do not form metastases." In harmony with this statement of Bruns is a case very recently recorded by Hochhaus[3] of three gliomas in

1. Borst: Die Lehre von den Geschwülsten, Wiesbaden, 1902, p. 254.
2. Bruns: Die Geschwülste des Nervensystems, ed. 2, Berlin, 1908, p. 6.
3. Hochhaus: Deutsch Ztschr. f. Nervenh., 1908, xxxiv, 185.

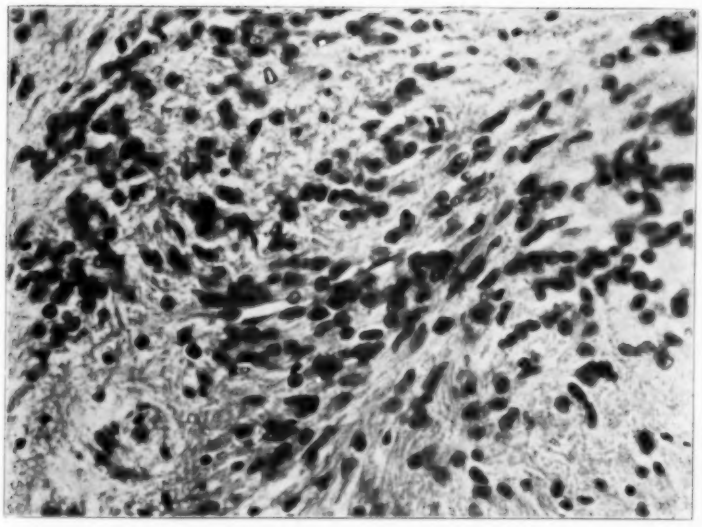

Fig. 4.—Photomicrograph of tumor in the fourth ventricle.

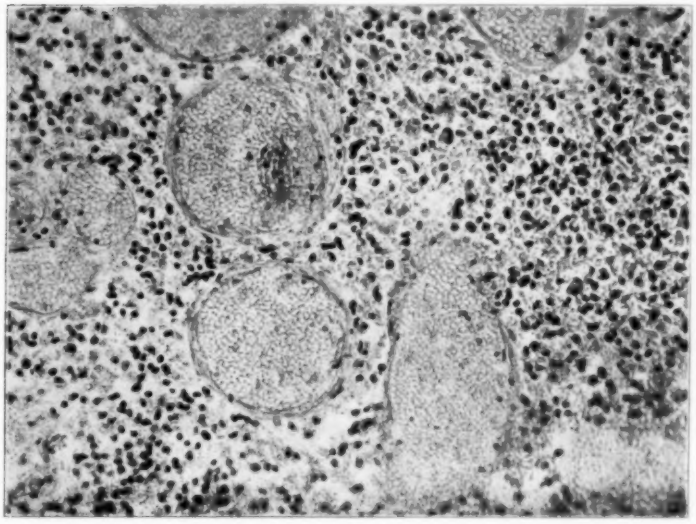

Fig. 5.—Photomicrograph of tumor in the left frontal lobe showing a very vascular area

one cerebral hemisphere, namely, a very large one, 20 cm. in length in the right hemisphere and small ones in the right frontal and temporal lobes.

Gliomatous, or "gliosarcomatous," invasion of the pia, the absence of which ordinarily constitutes one of the most characteristic features of glioma, has been described by Grund[4] and has recently been thoroughly discussed by Spiller.[5] Here he refers to a case previously reported by him[6] as sarcomatosis, which he now is convinced was one of multiple glioma. There were tumors in the lower part of the fourth ventricle, in both cerebello-pontile angles embedding the exit of many cranial nerves from the base of the brain, and numerous tumors in the spinal pia. He also considers as being multiple glioma a case reported by Spiller, Musser and Martin[7] in which there were two separate tumors, one filling the lower part of the fourth ventricle and extending downward on the cord as far as the sixth cervical segment, the other located on the lower part of the thoracic cord. Both have the structure of ependymoma and he considers the second one metastatic.

TUMORS OF THE FOURTH VENTRICLE.

The literature on tumors of the fourth ventricle now comprises about fifty cases, according to Arthur Stern[8], who gives a review of the literature down to the present and a report of a new case in a very recent article. Many varieties of tumor have been found, but glioma is by far the most frequent form. Thus, of thirteen well studied cases compiled by Linck,[9] seven were gliomas. Vigouroux[10] this year reports a case of papilloma growing from the chorioid plexus of the fourth ventricle, which is unique, as three years before the patient's death cerebrospinal fluid began to escape from the nose, resulting in complete relief from the headache.

Of especial interest is the tumor described by Muthmann and Sauerbeck,[11] as the illustration shows it to bear striking resemblance to the fourth ventricle tumor in my own case. It measured 4.3 by 3.2 cm.,

4. Grund: Deutsch Ztschr. f. Nervenh., 1906, xxxi, 283.
5. Spiller: Gliomatosis of the Pia and Metastasis of Glioma, Jour. Nerv. and Ment. Disease, May, 1907.
6. Spiller and Hendrickson: Am. Jour. Med. Sc., 1903, cxxvi, 10.
7. Spiller, Musser and Martin: Univ. Penn. Med. Bull., March and April, 1903.
8. Stern: Deutsch Ztschr. f. Nervenh., 1908, xxxiv, 195.
9. Linck: Beitr. z. path. Anat. u. z. allg. Path (Ziegler's), 1903, xxxiii, 98.
10. Vigouroux: Rev. neurol., 1908, xvi, 281.
11. Muthmann and Sauerbeck: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1903, xxxiv, 445.

filled the fourth ventricle completely and was lying free except for a band 3 mm. wide connecting it with the right restiform body. Unlike mine, however, it took its origin from the posterior medullary velum, and histologically it represented a much more highly differentiated type of glia than mine. In this case, as in that of Stern and my own, the brain was dry at the time of death, but there was distinct internal hydrocephalus. A good discussion of the symptomatology is found in the article by Stern,[8] who points out that the clinical picture is generally that of internal hydrocephalus. Symptoms may appear only a few weeks or a few days before death. Sudden death is very frequent and death usually, as in our case, is due to respiratory failure.

Optic neuritis is much less frequent than in cases of tumor in other portions of the brain. It was present in only ten of thirty-three compiled by Cimbal.[12] Stern summarizes the diagnostic points as follows: "Aside from focal symptoms on the part of the bulb and cerebellum, and general symptoms of increased intracranial pressure, we have as characteristic phenomena the occipital headaches, the stiff flexed neck, the periodical course and sudden death." Lumbar puncture in many of these cases, as in others of tumor in the posterior fossa, has had an unfavorable effect; undoubtedly because it upsets Nature's carefully established equilibrium of pressure in the neighborhood of the respiratory and other vital centers. In our case, as in that of Stern, the fluid obtained presented an increased amount of albumin and lymphocytes, findings which led me to a probable diagnosis of cerebral syphilis. In cases of cysticercus of the fourth ventricle, sixty-eight of which are compiled in another article by Stern,[13] lymphocytosis also has existed in the majority of the few cases in which the fluid has been examined. Hammer[14] has reported a case with the curious coincidence of cysticercus in the fourth ventricle and gliosarcoma in the left cerebral hemisphere.

34 Washington Street.

12. Cimbal: Virchow's Arch. f. path. anat., 1901, clxvi, 289.
13. Stern: Ztschr. f. klin. Med., 1907, lxi, 64.
14. Hammer: Prag. med. Wchnschr., 1889, xiv, 243.

CLINICAL NOTES AND PHYSICOCHEMICAL STUDY OF SALT ELIMINATION IN THE URINE OF AN INDIVIDUAL WITH GENERAL EDEMA OF OBSCURE ORIGIN, FOLLOWED BY CURE.*

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This case of general edema of obscure origin without evidence of kidney lesion is reported in part on account of its interest clinically and in part because of the unusual importance of the results of the physical and chemical examination of urine. Incidentally, therapeutic observations difficult of interpretation but apparently of some value are also presented.

CLINICAL REPORT (A. W. ELTING).

Patient.—G. H. R., aged 45, an experimental chemist by occupation, was first seen in July, 1907, at which time he complained of irritation of the throat, general debility, and inability to concentrate his attention on his work.

History.—His family and past history were negative, except that for the last ten years most of his time had been spent in a much vitiated atmosphere due to the decomposition at high temperatures of linseed oil, gums, resins and hydrocarbon compounds. These vapors are for the most part acid, readily form metallic salts, and are as a rule irritating to the urinary tract. The patient used alcohol and tobacco moderately and gave an indefinite and improbable history of chancre twenty years ago, with no subsequent luetic manifestations.

Onset of Disease.—He had noticed for several years past that when subjected to the fumes above described he would be troubled by irritation of the urinary tract and of the throat. During the winter of 1903 he first observed an occasional swelling of the palmar surface of the fingers, and about the same time some slight enlargement of the upper part of the abdomen. He also became fatigued on slight exertion and very languid. Moderate doses of blue mass relieved these conditions temporarily. In 1905 the feeling of lassitude became quite constant. He would arise in the morning feeling fairly well, but on moving about would soon become tired. He was also troubled with drowsiness during the day, sometimes falling asleep at his desk. Nervousness was an almost constant symptom, for which no definite cause could be assigned, and he suffered from slight lapses of memory and was at times much troubled with a cough. On retiring at night he would fall asleep for a short time and then awaken with a nervous start which would be followed by insomnia for the rest of the night. In April, 1907, he noticed some puffiness about the lower eyelids, which later extended to the temporal region. About this time he found that he could not lie with his head low in bed without experiencing a sensation in the ears similar to that caused

*This investigation was pursued under a grant made by the Committee on Scientific Research of the American Medical Association, and is from the Bender Laboratory, Albany, N. Y.

by water. When the patient was seen in July there was very slight puffiness about the lower eyelids and face, with moderate chronic laryngitis, but no other evidence of physical disorder. The usual urine examination at that time was negative. In August and September the edema increased somewhat in the face and extended to the neck, chest, upper part of the back and the upper extremities. He was seen again about Oct. 1, 1907, at which time the edema in the above-mentioned localities was quite pronounced and there was slight dyspnea and cyanosis. A suspicion of mediastinal tumor was entertained, but absolutely no physical evidence of such a condition could be detected. The urine examination was negative (chlorid elimination was not tested). The patient was advised to give up his work for a time and go to his home in Pennsylvania. This he did. About this time the cough became much aggravated and more paroxysmal in character, accompanied by vertigo and semi-unconsciousness for a few seconds. The patient also found it impossible to lie flat in bed because of dyspnea and was compelled to sleep propped up. About Oct. 15, 1907, the attacks of coughing became much more severe and breathing more labored; the expectoration was slight in amount and consisted of a frothy mucus. The edema gradually extended downward over the trunk, then involved the scrotum and finally, but gradually, the legs. The patient's condition became desperate because of the attacks of coughing, the dyspnea and the cyanosis, and with much difficulty he was brought from his home in Pennsylvania to St. Peter's Hospital, where he was admitted Oct. 30, 1907.

Condition on Admission.—This was alarming. Dyspnea was very marked and increased on the slightest exertion. Cyanosis was pronounced and there was a most extensive edema of the face, neck, chest, back and upper extremities, less marked over the lower part of the trunk, the scrotum and lower extremities. The patient suffered from frequent paroxysms of coughing, and at these times he would have mild convulsive seizures and become unconscious for a few seconds. It was impossible for the patient to lie down and he sat propped up in a chair. The edema was of a firm character and seemed to involve the muscles and deeper tissues rather than the subcutaneous tissues.

Physical Examination.—There was absolutely no evidence of any accumulation of fluid in the serous cavities. Examination of the heart and lungs was negative except for sibilant, sonorous and some small moist râles. The abdominal viscera were normal. The temperature was subnormal and the pulse about 100. The quantity of urine was much reduced, varying from 300 to 500 c.c. in twenty-four hours. The patient was extremely nervous and slept but little. His appetite was poor. The blood examination was negative. Satisfactory radiographs of the thorax were obtained, but these were normal and there was no evidence whatever of mediastinal tumor or aneurism. Nervousness was a constant and pronounced symptom, as was insomnia. The patient's condition for the first week after admission to the hospital was most desperate, chiefly because of the attacks of dyspnea and coughing, during which he would frequently lose consciousness. The appetite was very poor.

Treatment.—On admission to the hospital the patient was given large quantities of liquids and iodid of potash in increasing doses.

November 10: The administration of acetate of potash and infusion of digitalis apparently caused some increase in the volume of urine.

November 12: A steam bath was given without any evident increase in the perspiration, the patient's skin having been unusually dry at all times and perspiration evidently very much below the normal. Heroin in 1/12 grain doses seemed to be quite effectual in relieving the cough. He was unable to lie down and spent all his time propped up in a chair.

November 21: He suffered a very severe attack of dyspnea and became unconscious. Oxygen, amyl nitrite and nitroglycerin were freely used and resuscitated him. The patient was given an ounce of magnesium sulphate every other morning and the stools were quite watery in consequence.

November 25: He was placed on as nearly a salt-free diet as could be secured, and from this date until Feb. 1, 1908, a somewhat complete quantitative examination of the urine was performed daily, the results of which follow the clinical report.

November 27: The diuretic mixture was discontinued.

December 8: The patient was given potassium nitrate in 15 grain doses every three hours. As the result of the administration of this the volume of the urine increased until on December 12 it amounted to 3,225 c.c. (Table 2). Coincident with this there was a marked diminution in the edema and a decided improvement in the general condition. Attempts were also made to give the patient subcutaneous infusions of sterile water, but these had to be abandoned because of the great pain they occasioned. He was, however, given 12 ounces of sterile water by rectum each day. The potassium nitrate was discontinued on December 12 and was resumed on December 14, with but little effect on the volume of the urine, but the chlorid output was markedly increased.

December 13: The patient was given an artificial Nauheim bath and this was repeated on two successive days with apparently a marked softening and lessening of the edema and a decided improvement in the cough and dyspnea.

December 27: Another series of artificial Nauheim baths was given on alternate days with a lessening of the edema. About this time the patient was able to assume a somewhat reclining posture at night and gradually as his condition improved his position in sleeping approached more and more the horizontal. About Jan. 1, 1908, the patient began to take a few steps, but was easily exhausted and was very weak.

January 4: He experienced a very severe attack of coughing and dyspnea and the edema increased slightly.

January 20: A small fixed quantity of salt, 5 grams per diem, was added to the food, but the patient objected strongly, stating that it nauseated him. Gradually, however, he became accustomed to it and the dislike for salt disappeared.

Clinical Course.—The course of the edema was variable; as a rule, when the urine increased the edema decreased. The edema first disappeared from the chest, then the face and back, the legs and forearms being the last to yield. Gradually the patient was encouraged to take more exercise and to get out of doors for a short time each day. This seemed to exert a very beneficial effect on the edema, and the dyspnea and coughing seemed to vary with the edema.

Later Course.—The patient left the hospital on Feb. 1, 1908. At this time there was still some edema in the forearms and legs, and some dyspnea, which increased on exertion. His general condition was fairly good. His strength was greatly improved and he was voiding about a normal amount of urine. He was then able to sleep in the horizontal position and was decidedly less nervous. The week following discharge from the hospital was spent at his home. The urine varied from 600 to 900 c.c. in twenty-four hours, and the patient's appetite was somewhat improved. At the end of one week he started for Bermuda. The sea air increased the cough and expectoration somewhat, but the breathing was less labored. Shortly after arriving in Bermuda he was taken with a chill, followed by a fever which lasted for a day or two. He had great thirst and drank large quantities of water. At this time he had massage each day for three or four days and the urine rapidly increased to 3,000 c.c. in twenty-four hours. He was on a light diet with large quantities of fruit, especially oranges. From Bermuda he

went to Nassau, where the temperature was higher and where he was able to take more exercise and felt much better. The urine ranged from 1,500 to 1,800 c.c. daily. Early in March the patient returned to Pennsylvania, much improved in every way, the edema less marked, his strength greatly improved and with but little dyspnea on exertion. When the patient was seen June 10, 1908, there was but slight edema, traces being found in the neck, forearms, calves and about the ankles; this, as previously, seemed to be muscular rather than subcutaneous. The edema appeared to be more or less transitory. Sleeping in the sitting posture increased the edema of the legs, while sleeping in the recumbent posture increased it in the face, neck and arms. Exercise rapidly lessened the edema. The general health was good and the appetite was normal. Since the middle of February the patient has taken no medicine, except one ounce of Rochelle salts every other day and an occasional eight-grain blue mass pill. The cough has entirely ceased, except on severe exertion, and when it does occur it is without the previous spasmodic character. The patient has resumed part of his duties.

EXAMINATION OF THE URINE (H. C. JACKSON).

As stated in the clinical notes, a preliminary examination of a twenty-four-hour specimen of the urine on Nov. 21, 1907, showed a small volume of 340 c.c. with a normal specific gravity of 1025. Qualitative tests indicated that no pathologic substances were present. The first indication of an abnormality was shown on testing for chlorids by the addition of silver nitrate to the urine made acid with nitric acid. The slightest precipitate, amounting to only an opalescence, resulted, indicating a practical absence of chlorids. At this time the patient was living on the ordinary hospital diet. Orders were immediately given for the preparation of a special diet which was as nearly free from salts, especially sodium chlorid, as could be obtained. Fluids were given in as large quantities as possible. The regular examination and analysis of twenty-four-hour samples of urine began on Nov. 24, 1907, and continued until Feb. 1, 1908, in all ten weeks. The analysis consisted in the determination of the volume, specific gravity, total nitrogen according to Kjeldahl's method, chlorids by Volhard's indirect method, phosphates by titration with uranium nitrate and the depression of the freezing point $\triangle$ by means of the ordinary Beckmann apparatus. At various times during the period of observation the ammonia and uric acid were estimated and were found to be normal in amount and in percentage of total nitrogen. At no time could albumin or casts be detected. The whole time of observation has been divided into four periods of from ten to thirteen days each. The first represents the time during the change from the normal to salt-free diet and includes nine days on the latter diet. The second follows the first, after a lapse of three days, and consists of the days just before, during and after the administration of potassium nitrate during a salt-free diet. The third, with three days' interval, represents the effect of artificial Nauheim baths on the patient, who was still on the same diet. The fourth and last period begins after a lapse of eleven days, during which time the condition of the patient was steadily improving on the salt-free diet and continues during the period when an approximately normal diet was resumed. The patient, during the period of forced restraint from salt, developed a decided dislike to the condiment and it was only with considerable difficulty, by persuasion and by placing the salt in the food during preparation, that he was induced to take a definite amount (5 grams) each day during the final period of normal diet. The tables for the four periods follow, with the discussion of the important points brought out in each:

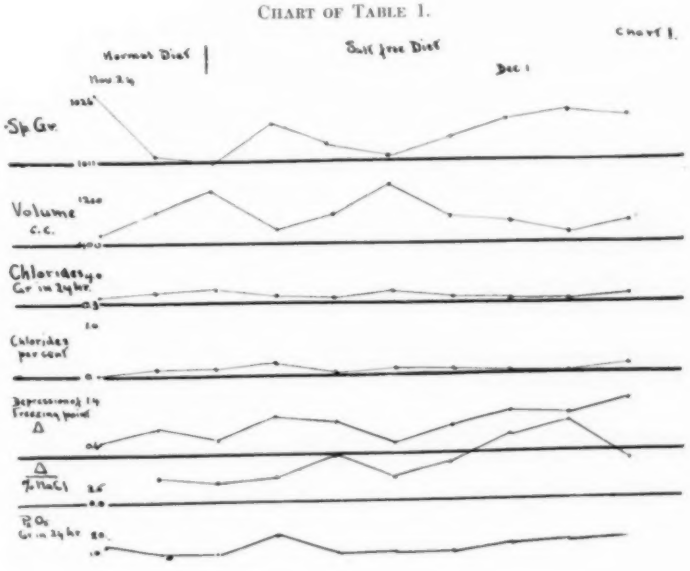
PERIOD I.

Previous to Nov. 24, 1907, the daily volume of the urine averaged from 150 to 300 c.c. and the administration of digitalis and potassium acetate and digitalin had little effect as regards the volume of output. It will be seen in the clinical

TABLE 1.

Date	Vol. cc.	Sp. Gr. 1.0—	Chlorids		P_2O_5 Grains	Δ	Δ / Na Cl	
			Grams	Per Cent.				
11 24	415	27	1.34	0.32	1.42	.....	....	Normal diet.
11 25	800	13	1.92	0.21	1.07	0.87	4.1	Normal diet.
11 26	1150	11	2.53	0.22	1.10	0.665	3.2	Salt-free diet.
11 27	515	20	1.43	0.27	1.81	1.085	4.0	Salt-free diet.
11 28	700	15	0.84	0.12	1.14	0.950	7.9	Salt-free diet.
11/29	1220	12	1.95	0.16	1.16	0.545	3.4	Salt-free diet.
11 30	650	16	0.91	0.14	1.21	0.865	6.1	Salt-free diet.
12 1	535	20	0.53	0.10	1.47	1.100	11.0	Salt-free diet.
12 2	....	..	....	....	....	.....	....	
12 3	365	22	0.29	0.08	0.66	1.090	13.6	Salt-free diet.
12 4	540	21	1.08	0.20	1.49	1.280	6.4	Salt-free diet.

CHART OF TABLE 1.



report that the administration of water on the salt-free diet benefited this condition somewhat, as the volume rose at times to almost the normal with the specific gravity only a little below the average. The absolute chlorid elimination averaged almost 2 grams on the normal diet. This amount fell gradually during the salt privation, although at times it reached nearly to the normal diet figures for this individual. It is interesting to note that the chlorid percentage output did not vary with the absolute output of chlorin or with the elimination of water, but with some few exceptional days remained between 0.16 and 0.32 per cent. (see also the first two days in Table 2). This fact seemed to indicate that during the period of hydremic plethora following the ingestion of larger quantities of water the blood was able quickly to resume its then normal osmotic concentration by drawing from the salt of the tissues, and that the filtrate passing through the glomerulus was constant in composition and was normally concentrated in the convoluted tubules. On the other hand, the depression of the freezing point runs parallel with the specific gravity and inversely as the volume and in no relation to the chlorid output, absolute or percentage. Evidently, then, the nitrogenous constituents (urea, uric acid, kreatinin, etc.) were being eliminated in normal manner and variations in their output and percentage relations were causing the ordinary changes in specific gravity and depression of the freezing point. Neglecting the abnormally low chlorid elimination, and hence low specific gravity in relation to the volume of urine excreted, the other physical factors reacted perfectly normally. Thus no evidence could be obtained in any way, at any stage of the investigation, that the renal function was affected in the slightest degree. The phosphoric acid elimination was somewhat below the average, but, when considered in connection with the diet and amount of nitrogen excreted, it was considerably above the normal. We believe that the high $\frac{\Delta}{NaCl}$ factor was without value as an indication of any disturbed circulatory, cardiac or renal lesion (Korânyi[1]), since this factor paralleled almost exactly the concentration of the urine as indicated by the specific gravity and depression of the freezing point.

PERIOD II.

On Dec. 9, 1907, the administration of potassium nitrate in doses of 15 grains every three hours was begun and continued for three days followed after one day's intermission by a second period of three days with similar treatment. During all this time the salt privation was continued. The nitrate was selected[2] since, according to Sollmann, sodium nitrate stands as one of the few diuretics which occasions an increased percentage output of sodium chlorid coincident to the diuresis. The explanation offered by Sollmann is that the nitrate replaces the sodium chlorid in the tissues, thus throwing the latter substance out of combination and allowing of its excretion. In view of the relatively small amounts of potassium nitrate administered and the tremendous elimination of sodium chlorid which it caused, such an explanation seems hardly probable or even possible. As

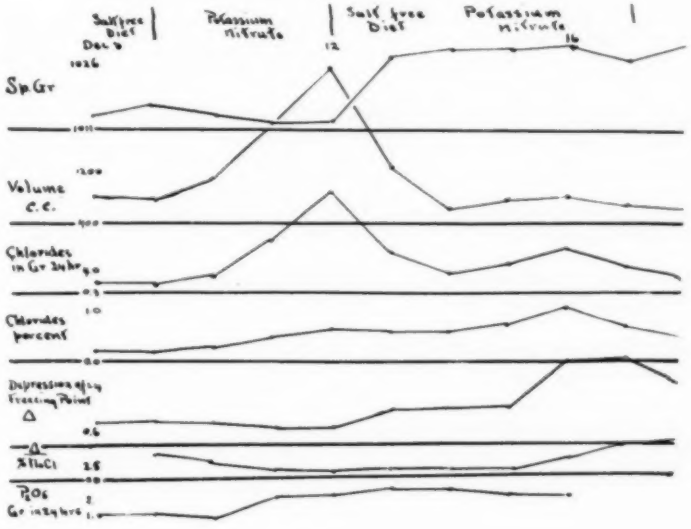
1. v. Korânyi, A.: Physiologische und klinische Untersuchungen über den osmotischen Druck thierischen Flüssigkeiten, Ztschr. f. klin. Med., 1897, xxxiii, i; 1898, xxxiv, i.

2. This substance was employed following the work of Sollmann (The Effect of Diuretics, Nephritic Poisons and Other Agencies on the Chlorids of the Urine, Am. Jour. Physiol., 1903, ix, 423), who showed the diuretic effect of sodium nitrate and its power to increase both the absolute and percentage elimination of chlorids. The potassium salt was chosen in the hope that the well-known effect of these salts in replacing sodium compounds in the body (Bunge) might aid in producing a favorable result.

TABLE 2.

Date.	Vol. cc.	Sp. Gr. 1.0—	Chlorids.		P_2O_5 Grams.	Δ	$\frac{\Delta}{Na\,Cl}$	
			Grams.	Per Cent.				
12/ 8	850	14	2.04	0.24	1.51	.....	....	Salt-free diet.
12/ 9	785	16	1.41	0.18	1.48	0.800	4.4	Salt-free diet.
12/10	1140	14	2.74	0.24	1.28	0.740	3.08	Pot. nitrate.
12/11	2110	12	8.86	0.42	2.00	0.650	1.50	Pot. nitrate.
12/12	3225	12	17.40	0.54	2.13	0.680	1.22	Pot. nitrate.
12/13	1300	26	6.50	0.50	2.08	0.775	1.55	Salt-free diet.
12/14	580	30	2.72	.47	2.24	.....	....	Pot. nitrate.
12/15	700	28	4.06	0.58	3.42	0.875	1.50	Pot. nitrate.
12/16	790	30	6.95	0.88	2.27	1.765	2.00	Pot. nitrate.
12/17	610	24	3.42	0.56	1.98	1.845	3.33	Salt-free diet.
12/18	525	28	2.10	0.40	....	1.535	5.45	Salt-free diet.
12/19	615	20	1.48	0.24	....	1.470	6.12	Salt-free diet.

CHART OF TABLE 2.



the table indicates, the potassium nitrate during the first period of ingestion caused a diuresis during which the volume increased to 3,225 c.c. on the last day; the specific gravity was not markedly lowered owing to the fact that the percentage output of sodium chlorid was doubled; on the last day the absolute excretion of chlorids reached 17.4 grams. The Δ remained unchanged; the increased concentration of the chlorids being counterbalanced by the decreased percentage elimination of the other soluble constituents of the urine, as is normally the case during diuresis. This again supports the view that the increased percentage output of chlorids is due to an increased ionic concentration of the blood in terms of this ion. The factor $\frac{\Delta}{NaCl}$ was reduced to the normal figures during this and the subsequent potassium nitrate period. The phosphoric acid output was somewhat increased in absolute amount, but the percentage figures were lowered during the diuresis. The second period of potassium nitrate ingestion differed slightly from the former in that the diuresis was not very evident; the increased chlorid output was quite pronounced, although not so marked as in the first period. This condition caused the Δ to increase and percentage of chlorid elimination to rise on one day to almost normal figures. During the six days of drug administration and the two single days following each period, 52.65 grams of sodium chlorid were excreted, and this during a salt-free diet.

If we consider the weight of the patient at 75 kilos and deduct therefrom the proportional fraction of this due to bone, by a simple calculation one can determine that the presence of these 52.6 grams of sodium chlorid in the body before its elimination would have been sufficient to increase the osmotic concentration of the fluids of the whole body equivalent to that of about a 1 per cent. sodium chlorid solution. This will serve to indicate the extreme state of hypertonicity which must have existed in the fluids of the body before the administration of the potassium nitrate and to which it is believed the edema was due.

This period of somewhat incomplete analytical results covers the time of gradual recovery with continued salt privation. During part of this time, beginning on Dec. 27, 1907, the patient was given a series of artificial Nauheim baths on alternate days, with the intention of stimulating the peripheral circulation. All previous attempts to cause sweating by hot baths, etc., had been fruitless. While the results are hard to explain, they are too evident to admit of doubt as to cause and effect. No change in the volume of urine was noticed, but the increased elimination of chlorids brought the percentage output almost up to normal on December 30 and to 1.7 per cent. on December 28. During the period between January 1 and 12 the effect of abstinence from sodium chlorid became evident in the extreme lowness of the absolute output, amounting on the average to only 0.45 gram. This can be seen on examination of the first three days, Table 4.

PERIOD IV.

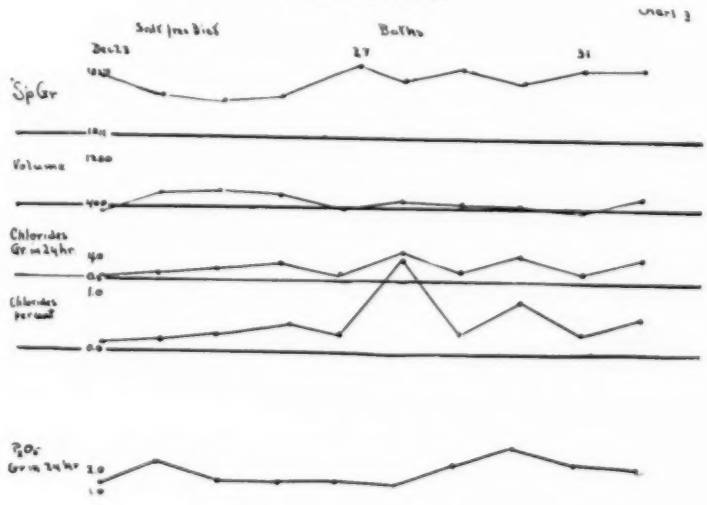
This table details the results of the commencement and continuance of a somewhat normal diet in which sodium chlorid was not excluded, but during part of which sodium chlorid was administered in 5-gram amounts *per diem*. The first ten days in the table are continuous; then follows a lapse of four days, and a subsequent period of three days is added in order to show the effect of the normal diet two weeks after its commencement. Finally, there follows the results of a partial examination of the urine of the same individual on May 19, 1908, or three and one-half months subsequent to the time when the patient left the hospital (Feb. 1, 1908).

The figures for this period indicate that, while the volume of the urine had not assumed normal figures, the specific gravity was much higher with the same volume than was the case before the treatment began (Table 1). As striking evidence in favor of the view that the edema was set up by chlorid retention, there

TABLE 3.

Date.	Vol. cc.	Sp. Gr. 1.0	Chlorids.		P_2O_5 Grams.	
			Grams.	Per Cent.		
12/23	347	25	0.5	0.14	1.37	Salt-free diet.
12/24	645	30	1.2	0.19	2.16	Salt-free diet.
12/25	705	19	2.1	0.30	1.37	Salt-free diet.
12/26	615	20	3.0	0.48	1.30	Salt-free diet.
12/27	400	27	1.2	0.30	1.25	Salt-free diet.
12/28	525	21	8.82	1.70	1.60	Salt-free diet + Nauheim bath.
12/29	475	26	1.5	0.31	1.59	Salt-free diet.
1/30	480	23	4.2	0.88	2.19	Salt-free diet + Nauheim bath.
12/31	360	28	1.4	0.35	1.40	Salt-free diet.
	610	28	3.7	0.60	1.16	Salt-free diet + Nauheim bath.

CHART OF TABLE 3.



must be pointed out the tenacity with which the body has retained the chlorids in spite of deprivation of these salts; thus, after about seven weeks of salt-free diet, the body, even at that time, was not in a state of chlorid hunger, since the addition of 5 grams of salt to the diet caused the elimination, after three days, of over this amount and within the week following the body was almost in exact sodium chlorid equilibrium.

That the absolute and percentage output of sodium chlorid have not reached the normal figures is to be attributed to the fact mentioned above, that the patient, on being allowed to resume a normal diet, complained that salt nauseated him and refused to eat foods which tasted at all salty. The $\frac{\Delta}{NaCl}$ and the factor $\frac{\Delta}{\text{——}}$ rapidly assumed normal figures after the establishment of the normal diet and have remained so ever since. The phosphoric acid elimination is now well within normal limits.

On the whole, the examination of the urine the day before the patient left the hospital and three and one-half months after shows it to be practically normal when the character of the diet is taken into consideration.

DISCUSSION.

It seems evident that the appearance of the edema noticed in this case was accompanied by a diminished elimination of chlorids; whether this was the result of the edema or its cause is difficult to prove, especially on account of the fact that it was impossible to obtain any of the patient's blood for examination and comparison with the urinary findings. In particular cases of edema associated with certain renal lesions the cause is ordinarily attributed to a deficient eliminating power of the kidney for chlorids. At no time before or during the progress of the disease did any evidence of renal deficiency exist. Apparently, with an increased concentration of the blood for chlorids, there followed an augmented output of these ions. It seems reasonable therefore that the discussion of the renal function in this connection may be excluded.

It is impossible at this time to enter into a complete exposition of the various theories which have been advanced to explain salt retention in relation to hydrops. The subject and its literature have been well covered by Georgopulos[3] and by Christian[4]. The principal contention rests on the question whether the salt retention is the cause or the result of the appearance of the hydrops. Strauss,[5] Widal,[6] Halpern[7] and Cas-

3. Georgopulos: Experimentelle Beiträge zur Frage Nierenwassersucht, Ztschr. f. klin. Med., 1906, lx, 411.

4. Christian, H. A.: Experimental Nephritis, Boston Med. and Surg. Jour., 1908, clviii, 416, 452.

5. Strauss: Therap. d. Gegenwart, 1902, iv, 444; 1903, v, 193.

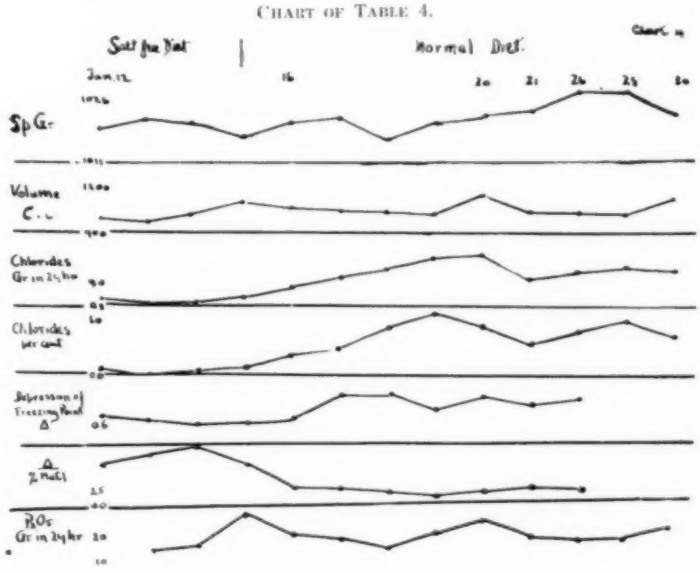
6. Widal: La cure de déchlorination, Bull. méd. des hôp., Paris, 1903, xx, 773, 990.

7. Halpern: Beiträge zur Frage des Verhaltens der Chlorid im Körper, ihre Berzieheng zur Oedembildung und ihre Bedentung fur die Diätetik bei Nephritis. Beitr. z. wissensch. Med. u. Chem. (Festschr. f. Salkowski), Berlin, 1904.

TABLE 4.

Date	Vol. c.c.	Sp. Gr. 1.10—	Chlorids		P_2O_5 Grams	Δ	Δ NaCl	
			Grams	Per Cent.				
1/12	665	18	1.10	0.16	....	1.135	7.08	Salt-free diet.
1/13	605	20	0.38	0.06	1.47	.....	.....	Salt-free diet.
1/14	710	19	0.48	0.09	1.64	0.975	10.80	Salt-free diet.
1/15	935	16	1.30	0.14	2.72	0.990	7.07	Normal diet.
1/16	805	19	2.86	0.35	2.03	1.080	3.08	Normal diet.
1/17	755	20	4.23	0.56	1.86	1.480	2.65	Normal diet.
1/18	715	15	5.58	0.78	1.47	1.450	1.86	Normal diet + 5 grams NaCl.
1/19	675	19	7.310	1.09	....	1.200	1.10	Normal diet + 5 grams NaCl.
1/20	975	22	7.60	0.78	2.42	1.400	1.80	Normal diet + 5 grams NaCl.
1/21	695	23	3.75	0.54	1.79	1.250	2.34	Normal diet + 5 grams NaCl.
....	....	..	.....	....	....	.....	.....	
1/28	665	26	4.67	0.70	1.65	1.345	1.92	Normal diet + 5 grams NaCl.
1/28	660	26	5.54	0.84	1.67	.....	.....	Normal diet + 5 grams NaCl.
1/30	800	21	5.01	0.56	2.22	.....	.....	Normal diet + 5 grams NaCl.
.. ..	....	..	.....	....	....	.....	.....	
5/19	1170	25	7.76	0.66	2.45	.....	.....	Normal diet.

CHART OF TABLE 4.



taigne,[8] among others, believe that the salt retention in the tissues is primary to the retention of water; the latter observer bases his views on experiments in which saline was injected into normal animals and those with experimental nephritis. The urine in both cases showed no difference. But if sound and diseased animals were bled and saline injected very soon afterwards, the blood of the nephritics contained less salt. The fact that in certain febrile conditions there exists a retention of chlorids without evident renal disturbance is also cited as evidence of the primary nature of the retention. In these cases edema does not necessarily result; and this seems sufficient reason to believe that the factor of permeability of the epithelial lining of the capillaries forms a not unimportant adjunct to the whole process. Müller[9] advances this view and considers that the hydrops is due to an increased permeability of the blood vessels due to certain toxic products in the blood. This conception receives support from Cohnheim and Lichtheim,[10] who showed that subcutaneous edema only followed saline injection when the skin had been irritated in any way, and the results of Magnus with chloroform irritation pointed in the same direction.

In view of the extremely obscure etiology of the case under discussion it would seem to us that a combination of Müller's explanation and that of increased combining power of tissues for chlorids must form the basis for any reasonable explanation of the condition. Nothing in the history of the case points to any anatomic lesion which might account for the hydrops. The appearance in the blood of toxic products inhaled through the lungs as the result of continued sojourn in the vitiated air of a chemical laboratory might readily set up changes in the epithelial lining of the capillaries rendering them more permeable and at the same time bring about changes in the protoplasm of the cell by which the combining power of the proteins would be increased. This in turn would cause an increased osmotic concentration in the cells and as an attempt to reduce this, water would be drawn from the blood. This view would explain, on the one hand, the failure of digitalis and similar agents to cause a diuresis, the dryness of the skin and inability to produce sweating in hot baths; and, on the other hand, the beneficial effects of artificial Nauheim baths in stimulating the cutaneous circulation and capillary

8. Castaigne: Le rôle du reins dans la rétention chlorurée, Semaine méd., 1903, xxiii, 309; 1905, xxv, 472.

9. Müller: Morbus Brightii, Verhandl. d. deutsch. path. Gesellsch., 1905, ix, 64.

10. Cohnheim, J., and Lichtheim, L.: Ueber Hydrämie und hydrämisches Oedem, Virchow's Arch. f. path. Anat., 1877, lxix, 106.

epithelium, and the effect of potassium nitrate in starting the replacement of the combined chlorids by means of the nitrate, after which the reduction in ionic concentration, followed by means of mass action. Bunge[1] might be more prone to explain this last process as a replacement of the sodium ion by potassium.

Finally, it must be mentioned that Georgopulos and others present strong arguments against the view that the water retention is secondary to the salt retention. They believe that the kidney becomes more impermeable to water, a hydremic plethora results and the tissues become overladen with water as a result. Georgopulos states with truth that an increase in the salt content of the tissues during the so-called salt retention has never been proved by experiment. This, however, may have been due to faulty methods. At present it is impossible to decide these disputed points. Nevertheless, we feel inclined to believe, from all the evidence which we have been able to obtain from the results derived from the study and treatment of the case, that the above explanation is possible and most probable and that we are dealing with a case of chlorid retention brought about by the action of some general toxemia which occasioned an increased permeability of the capillaries to chlorids and an augmented combining power of the protoplasm for these ions.

11. Bunge: Lehrbuch der physiologischen Chemie, Leipsic, 1900.

AN UNUSUAL PAROXYSMAL SYNDROME, PROBABLY ALLIED TO RECURRENT VOMITING,

WITH A STUDY OF THE NITROGEN METABOLISM.*

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The case here recorded, though still an unsolved diagnostic problem, seems from two standpoints of sufficient interest to justify publication: first, as presenting a clinical syndrome unique in our experience; second, as affording an unusual opportunity for the study of certain features of the nitrogen metabolism in fever of short duration.

HISTORY OF CASE.

The *patient*, a Jewish schoolgirl of 16, without special neurotic inheritance, was referred to me by Dr. Halpert, of Scranton, Pa. She had had measles and diphtheria, but no other illnesses. All her life she had suffered from recurring attacks of a peculiar nature, the description of which, by her family, tallied exactly with those we subsequently observed. The mother said that she had noted the first attack when the patient was two weeks old. In earlier life the frequency was about once a month; the longest interval of freedom ten weeks. For a year attacks had come weekly; for three months, every Friday, with absolute periodicity. We had her under observation Nov. 6 to Dec. 2, 1907, and April 7 to May 5, 1908, with a careful record of the intervening period. In the six months there were fourteen attacks, five severe, and nine mild.

THE ATTACK EXHIBITS THREE STAGES.

1. *Prodromal period*, characterized by uneasiness, loss of appetite, and epigastric or abdominal discomfort, lasting four to twelve hours. This stage is occasionally protracted and may pass off without an attack.

2. *Crescendo period*, in which there is rapid increase in all symptoms: prostration, pain, fever, tachycardia, and polynuclear leucocytosis. The pain is chiefly abdominal and is colicky, but may also be referred to one or the other shoulder or hip, even to the feet. Occasionally there is headache. There is abdominal rigidity and tenderness, the latter varying in localization, but situated usually to one side of the umbilicus. The maximum temperature noted was 104°; pulse 140; leucocytes 28,800. There is complete anorexia and marked salivation; in severe attacks constant nausea and retching, with vomiting once or twice at the height of the attack. Vomitus consists of the previous meal with mucus and free hydrochloric acid, and in milder attacks vomiting does not occur. The duration of this stage is eight to sixteen hours.

3. *Period of recovery* with rapid subsidence of all symptoms; pain first, then fever; rapid pulse and leucocytosis last. Within twelve hours the temperature reaches normal; the patient feels well and has a voracious appetite. The loss of weight in a severe attack is four to five pounds, regained within a few days.

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*Read at the meeting of the Association of American Physicians, Washington, D. C., May 12, 1908.

Polynuclear leucopenia immediately follows the attacks, counts as low as 30 per cent. of polynuclear cells in a total count of 9,600, and of 36 per cent. in 6,900, having been recorded.

The severe attacks are characterized by the seeming intensity of the abdominal pain, great prostration and restlessness, constant straining and retching, and a very rapid pulse. The fever, while usually highest in the severe attacks, has borne no constant relation to the other symptoms. Abdominal rigidity and tenderness are sometimes as extreme as in general peritonitis, but the location of the maximum tenderness is variable. At no time has much tenderness been noted at McBurney's point. Dr. Brewer, who saw her in one attack, with reference to exploratory laparotomy, could find no definite localizing phenomena.

One striking feature of the attacks has been the invariable complaint of great pain in some other portion of the body, usually one or the other shoulder or hip.

Salivation is a regular accompaniment of the attacks, and the saliva is quite strongly acid. The tongue is heavily coated and the breath heavy, but never the so-called acetone breath. The vomitus was examined in three paroxysms. In one it was merely bile-stained fluid with mucus, and contained no free hydrochloric acid. In the other two it was the remains of previous meals and showed a considerable free hydrochloric acid content, 20 and 22 respectively, in a total acidity of 60 and 84.

The *urine* was somewhat reduced in quantity during the attacks, but never deposited urates or other crystals. After the two severest attacks it showed a mere trace of albumin, without casts. There has never been sugar. Marked indicanuria occurred at times during the second period of observation, especially accompanying the attacks. The behavior of the acetone bodies was instructive. During the autumn, while the patient was on a quantitative diet, which was forced as much as possible during the attacks, no Gerhardt reaction ever appeared in the urine. There was an occasional Legal reaction, unassociated with the paroxysms. In the second period the patient was not required to resume food after the attack until she wished it, and usually took practically nothing for two days. During these attacks diacetic acid developed in considerable amount, disappearing a few days later. The acidosis she exhibited, therefore, was mainly due to carbohydrate starvation, though apparently not wholly explained by this factor, as will be seen from its incidence on the charts. One of us has observed a severe case of recurrent vomiting persisting into adult life, in which the acidosis was distinctly an inanition phenomenon, secondary to the attacks. We believe that too little attention has been paid to the factor of carbohydrate starvation in the reports of recurrent vomiting, which have made acetonemia so important a feature of the underlying metabolic disorder.

Physical examination during the intervals showed only a persistently coated tongue, rather copious saliva, moderate secondary anemia, and slight hyperchlorhydria. The girl weighed from 100 to 105 pounds. Heart, lungs, liver, spleen and kidneys showed no abnormality. The abdomen was soft and painless. The stomach, on inflation, extended from two inches below the ensiform to one inch above the umbilicus; its capacity was 1,000 c.c. The fasting contents in the morning were 40 c.c. of bile-tinged fluid, with a total acidity of 55; free hydrochloric acid, 15=0.05 per cent. After an Ewald test breakfast 140 c.c. were obtained, with only moderate admixed mucus. Total acidity was 82; free hydrochloric acid, 58 = 0.21 per cent. There was no lactic acid. Starch conversion was very slight. The bowels moved regularly, and the stools were normal. Blood examination, November 6, showed hemoglobin 75 per cent.; red cells, 5,368,000; white cells, 8,800; polynuclear neutrophiles, 50 per cent.; polynuclear eosinophiles, 2 per cent.; small lymphocytes, 42 per cent.; large lymphocytes, 5.5 per cent.; mast cells, 0.5 per cent. The patient's pupils were moderately dilated and reacted

promptly to light. The knee-jerks were readily obtained with Jendrassik reinforcement.

No *treatment* has had a definite influence either on the attacks, or in diminishing their frequency. Previous to our study, the patient had been treated by a well known neurologist, apparently as a psychoneurotic. She had, at another time, tried daily lavage of the stomach for many weeks. We were unable to abort the attacks by lavage of the stomach, by free purgation, or by alkalies in large doses. For a time the continued use of the lattter, with iron and tonics, seemed to benefit her; but the attacks again recurred. While on a diet of milk, eggs, rice, bread and butter, of 2,350 calories, they were more frequent. The strong suggestion that we were curing her had no therapeutic efficacy.

DIAGNOSTIC POSSIBILITIES.

At the end of six months' observation we are unable to bring forward any direct evidence as to the causation or the real nature of the attacks, which continue to interfere seriously with the normal life and comfort of this patient, though she enjoys reasonable health between them. We have been unable to find a similar syndrome described in the literature, though a careful search is almost out of the question, since one must be in doubt under what index classification it might be hidden. There remains, then, only the unsatisfactory method of reasoning from analogy, in assigning such a case to even a general category. The diagnostic possibilities seem to us to group themselves under three heads:

1. A *recurring infectious syndrome,* due to a persistent inflammatory focus, with occasional absorption phenomena. The intermittent fever of biliary obstruction is the best analogue of this type. Recurring appendicitis, and the exacerbations of fever so often seen in connection with old tuberculous sinuses, are common examples.

2. A *recurring toxemic syndrome,* allied with such definite, but still unexplained, conditions as gout, recurrent vomiting, or perhaps migraine.

3. A *recurring nervous crisis.* The gastric crises of tabes have many features in common with our patient's attacks. Epilepsy is the standing witness to our inability to penetrate beneath the surface of a paroxysmal affection of every day occurrence and prehistoric origin. Possibly migraine should be placed in this category. Recurrent vomiting we are unwilling to consider a neurosis, though Fischl[1] inclines to the view that it is of hysterical nature. Few Americans, we take it, will agree with him. We must admit, however, that no sharp dividing line can be drawn between conceptions based on so little of known fact as are the so-called neuroses and toxemias; neither is it possible yet to discriminate

1. Fischl, R.: Pfaundler and Schlossmann's Handbuch der Kinderheilkunde, Leipzig, 1906, ii, 164.

between the infectious or the metabolic origin of the poison at work in such a recurring affection as Henoch's purpura.

Our personal leaning is toward considering the syndrome a toxemic one, of endogenous origin. The strongest argument in favor of its being due to an undiscovered focus of infection is the leucocytosis; but we know that aseptic wound fever, and even acute uremia, the latter certainly a toxemia, may produce a marked leucocyte increase. We wish to call special attention to the failure of practically all observers to report blood counts in cases of recurrent vomiting. We have been able to find but a single count, 10,000, in the case of a child of nine years.[2] A knowledge of the behavior of the white blood cells in this affection would be of service in deciding whether the syndrome we have described, which presents many points of similarity with certain cases of recurrent vomiting, may fairly be considered an allied affection.

It seems most unlikely that any inflammatory focus could continue for so many years to produce exactly similar attacks, without leading to more serious consequences, or giving other evidences of its existence. It is perhaps conceivable that a pancreatic calculus, nearly blocking a small branch of the duct of Wirsung, might give rise to such intermittent symptoms, but it seems highly improbable.

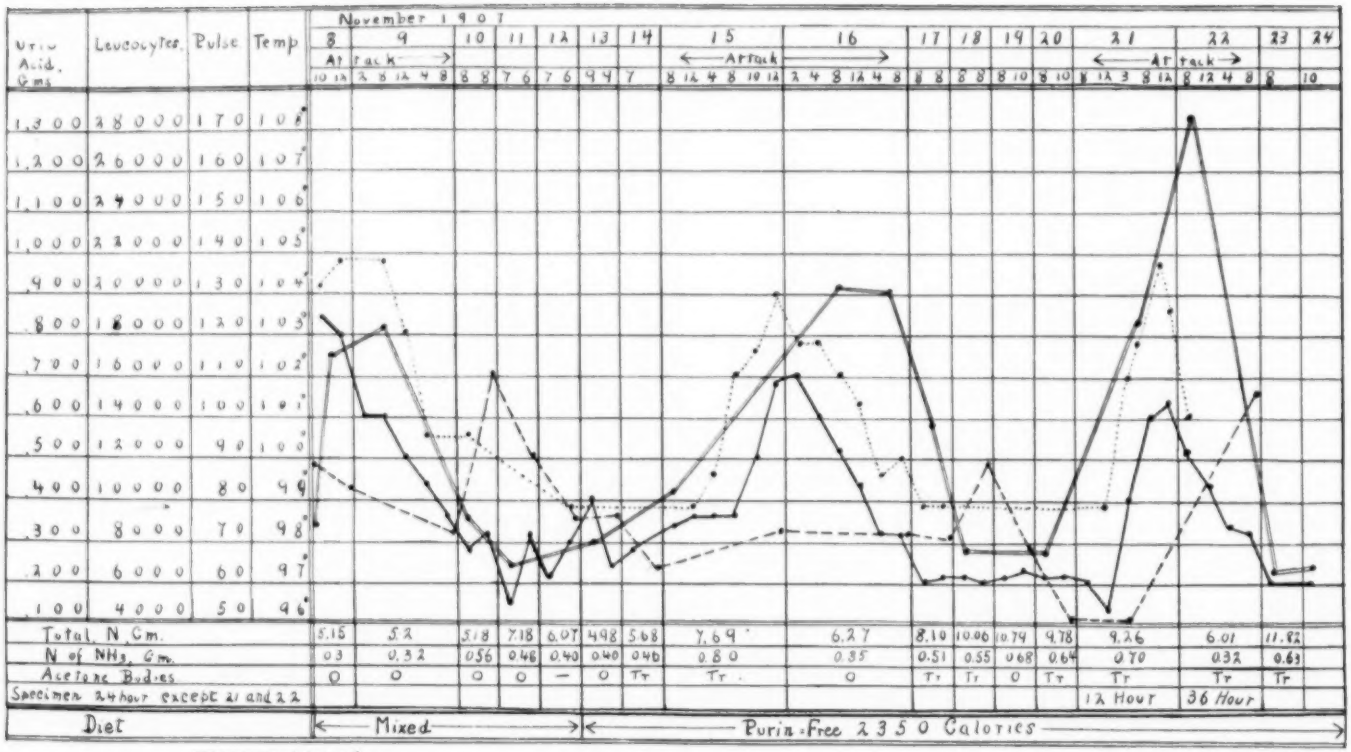
As for the ubiquitous diagnosis for all unexplained crises, hysteria, we think that scarcely warrants serious consideration. Hysterical pain is common; hysterical fever may exist; hysterical leucocytosis seems out of the question.

THE NITROGEN METABOLISM, WITH ESPECIAL REFERENCE TO URIC ACID AND KREATININ.

A study of the urinary nitrogen, during the two periods of observation, was made by Dr. Mosenthal, in the Laboratory of Biological Chemistry, Columbia University, at the College of Physicians and Surgeons, and we desire to express our appreciation of the help thus afforded us by Professor Gies.

During both periods the total nitrogen was determined by Kjeldahl's method, urea and ammonia by Folin's, and uric acid by the Folin-Hopkins method. During the second period kreatinin was also estimated by Folin's method with the Du Bosc colorimeter, acetone being first removed by precipitation with an alkalinized iodin solution, the urines which did not give an acetone reaction being treated in an exactly similar

2. Capito: Centralbl. f. inn. Med., 1907, xxviii, 1019.



Leucocytes.
Temp.
Uric Acid.
Pulse.

Chart I

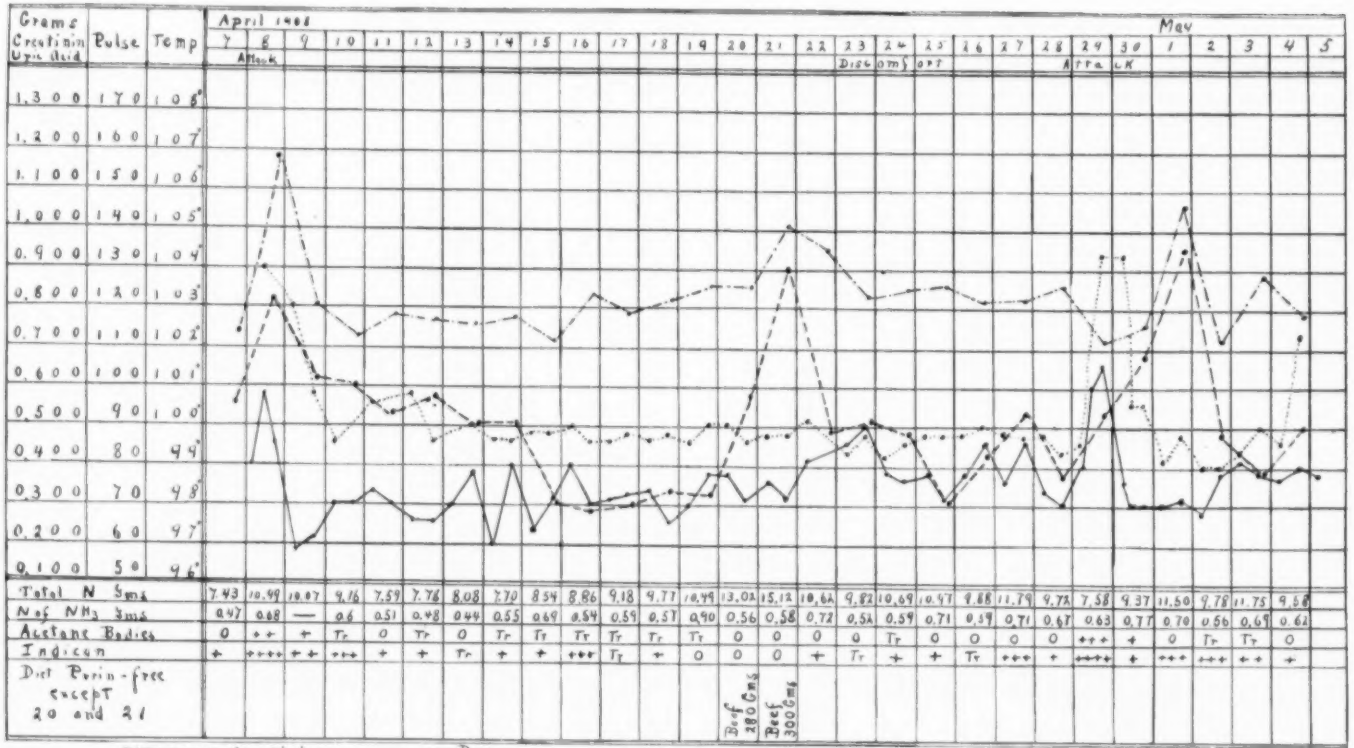

Grams Creatinin Urea acid
Pulse
Temp
April 1908
May
7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 1 2 3 4 5
Attack
Discharged
Attack
1.300 170 105°
1.200 160 107°
1.100 150 106°
1.000 140 105°
0.900 130 104°
0.800 120 103°
0.700 110 102°
0.600 100 101°
0.500 90 100°
0.400 80 99°
0.300 70 98°
0.200 60 97°
0.100 50 96°
Total N 5ms 7.43 10.49 10.07 9.16 7.59 7.76 8.08 7.70 8.54 8.86 9.18 9.77 10.49 13.02 15.12 10.64 9.82 10.69 10.47 9.88 11.79 9.73 7.58 9.37 11.50 9.78 11.75 9.58
N of NH3 5ms 0.47 0.68 — 0.6 0.51 0.48 0.44 0.55 0.69 0.84 0.59 0.57 0.90 0.56 0.58 0.72 0.54 0.59 0.71 0.59 0.71 0.67 0.63 0.77 0.70 0.56 0.69 0.62
Acetone Bodies 0 ++ + Tr 0 Tr 0 Tr Tr Tr Tr Tr Tr 0 0 0 0 Tr 0 0 0 0 +++ + 0 Tr Tr 0
Indican + ++++ +++ +++ + + Tr + + +++ Tr + 0 0 0 + Tr + + Tr +++ + ++++ + +++ +++ ++ +
Diet Purin-free except 20 and 21
Beef 280 Gms
Beef 300 Gms
Creatinin. Pulse.
Urea Acid. Temp.

Chart II

TABLE 1.

Date.	Sp. Gr. Volume in c.c.	Total Nitrogen, gm.	Urea, gm. Urea —N.	Ammonia, gm. Ammonia —N.	Uric Acid, gm. Uric Acid —N.	Undetermined —N.	Acetone. Diacetic Acid.	Indican.	In Per Cent. of Total Nitrogen.				Diet.
									Urea.	Ammonia.	Uric Acid.	Undetermined —N	
November 7....	1018 960	5.15	8.93 4.18	.36 .30	.48 .16	.51	0 0	.....	81.0	5.7	3.1	10.2	Mixed.
November 8....	1022 840	5.20	9.11 4.26	.39 .32	.43 .14	.48	0 0	.....	81.1	6.2	2.7	10.0	Attack
November 9....	1014 830	5.18	8.54 3.99	.68 .56	.34 .11	.52	0 0	+	77.0	10.7	2.2	10.1	Attack.
November 10....	1020 630	7.18	12.42 5.81	.58 .48	.71 .24	.65	0 0	Trace.	80.9	6.6	3.3	9.2	Mixed.
November 11....	1019 630	6.07	10.49 4.90	.49 .40	.50 .17	.69	....	.....	80.7	6.6	2.8	9.9	Mixed.
November 12....	1014 1220	4.98	7.72 3.61	.49 .40	.35 .12	.85	0 0	++	72.5	8.1	2.4	17.0	Mixed.
November 13....	1013 1820	5.68	9.90 4.63	.56 .46	.35 .12	.47	Trace. 0	+	81.4	8.1	2.0	8.5	Purin-free.
November 14....	1014 1800	7.09	13.27 6.20	.97 .80	.24 .08	.61	Trace. 0	0	80.6	10.4	1.1	7.9	Purin-free.
November 15....	1018 1180	6.27	11.43 5.34	.43 .35	.33 .11	.47	0 0	0	85.1	5.6	1.7	7.6	Attack.
November 16....	1013 1320	8.10	14.77 6.90	.62 .51	.32 .11	.58	Trace. 0	0	85.2	6.3	1.3	7.2	Attack.
November 17....	1016 1020	10.06	18.72 8.75	.67 .55	.31 .10	.66	Trace. 0	0	87.0	5.4	1.0	6.6	Purin-free.
November 18....	1018 1220	10.79	19.69 9.16	.83 .68	.49 .16	.79	0 0	Trace.	84.9	6.3	1.5	7.3	Purin-free.
November 19....	1014 2100	9.78	18.14 8.48	.78 .64	.28 .09	.57	Trace. 0	0	86.7	6.6	.9	5.8	Purin-free.
November 20....	1010 2380	9.26	18.02 8.42	.86 .70	.09 .03	.11	Trace. 0	0	91.0	7.6	.3	1.1	Purin-free.
November 21*...	1013 1250	6.01	11.20 5.23	.38 .32	.11 .04	.42	Trace. 0	Trace.	87.1	5.2	.6	7.1	Attack.
November 23†...	1016 1520	11.82	21.74 10.16	.76 .63	.66 .22	.81	Trace. 0	++	85.9	5.3	1.9	6.9	Attack.

* Twelve-hour specimen. † Thirty-six-hour specimen.

manner. All analyses were made in duplicate, and repeated where any suspicion of inaccuracy seemed justified.

During the first period the diet was the ordinary mixed diet of the patient until November 13, after which she took a purin-free diet of 1½ quarts milk, 5 eggs, 6 ounces bread, 2 ounces butter, and ¼ pound cooked rice, yielding 2,350 calories. As this became very distasteful, during the second period a larger variety of purin-free and kreatinin-free foods was allowed in addition, such as hominy, oatmeal, macaroni, cheese, apples, oranges, and desserts made from milk, eggs and sugar; and the quantities recorded. This diet was begun two days before the first observation and, except for the test beef days noted, was continued until the end of the period. During attacks only a few ounces of milk were taken, and the vomiting in some made any attempt at a true nitrogen balance impossible, so that the nitrogen of the feces was not estimated.

The results are given in tabular form, and the relation of the uric acid and kreatinin output to the attacks is also shown strikingly on the charts.

The total nitrogen throughout tended to be low, especially during the first period before the patient was put on a quantitative diet. Associated with this were low figures for urea and rather high for ammonia, corresponding with Folin's[3] findings in normal persons on diets poor in nitrogen. During the second period the nitrogen averaged higher, the urea nitrogen seldom below 85 per cent., but the ammonia nitrogen still a trifle high, usually above 6 per cent. We are unwilling to attach any significance, however, to these small differences.

A sharp nitrogen loss accompanied the attacks, as would be expected, the largest deficit noted, 9.5 gm., having been on April 8. After this there was a steady nitrogen retention until April 27, then two days near equilibrium, then a marked loss again for four days. The greatest gain was on the two beef days, about 6 gm. each day.

The main interest centers in the uric acid and kreatinin figures. Both, as will be seen at a glance, rose sharply with the attacks. The uric acid, in addition, throughout the whole study, showed wide variations for endogenous excretion, in fact as wide as Kaufmann and Mohr,[4] and von Noorden,[5] describe in the subjects of true gout. A moderate fall in the uric acid output also seemed to precede the attacks.

For this reason a test of the patient's tolerance for exogenous purins

3. Folin, O.: Am. Jour. Physiol., 1905, xiii, 66.
4. Kaufmann and Mohr: Deutsch. Arch. f. klin. Med., 1902, lxiv, 586.
5. von Noorden: Handbuch der Pathologie des Stoffwechsels, ed. 2, 1907, ii, 153.

TABLE 2.

Date.	Sp. Gr. Volume in c.c.	Total Nitrogen, gm.	Urea, gm. Urea—N.	Ammonia, gm. Ammonia—N.	Kreatinin, gm. Kreatinin—N.	Uric Acid, gm. Uric Acid—N.	Undetermined—N.	Acetone. Diacetic Acid.	Indican.	In Per Cent. of Total Nitrogen.					Diet.
										Urea.	Ammonia.	Kreatinin.	Uric Acid.	Undetermined—N.	Purin-free and Kreatin-free.
April 7.....	1025 700	7.43	13.64 6.37	.58 .48	.74 .28	.56 .19	.13	0 0	++	85.8	6.4	3.7	2.5	1.6	Attack.
April 8.....	1030 620	10.99	19.63 9.17	.83 .68	1.19 .44	.82 .27	.43	++ +	++++	83.5	6.2	4.0	2.5	3.8	Attack.
April 9.....	1020 640	10.07	9.28*	.....	.80 .30	.62 .21	.28	+ Trace.	++	92.2	.....	2.9	2.0	2.9	.....
April 10.....	1016 820	9.16	16.67 7.79	.73 .60	.73 .27	.60 .20	.30	Trace. Trace.	+++	85.0	6.5	3.0	2.2	3.3	.....
April 11.....	1020 610	7.59	12.99 6.07	.62 .51	.78 .29	.54 .18	.54	0 0	+	79.9	6.7	3.8	2.4	7.2	.....
April 12.....	1020 660	7.78	13.07 6.53	.58 .48	.77 .29	.57 .19	.29	Trace. 0	+	84.0	6.1	3.7	2.4	3.8	.....
April 13.....	1018 950	8.08	15.10 7.05	.53 .44	.76 .28	.49 .16	.15	0 0	Trace.	87.3	5.5	3.5	2.0	1.7	.....
April 14.....	1017 840	7.70	14.20 6.59	.67 .55	.78 .29	.50 .17	.10	Trace. 0	+	85.6	7.2	3.8	2.2	1.2	.....
April 15.....	1012 1600	8.54	15.66 7.32	.83 .69	.72 .27	.30 .10	.16	Trace. 0	+	85.7	8.0	3.2	1.2	1.9	.....
April 16.....	1019 1190	8.86	16.80 7.85	.66 .54	.85 .32	.28 .09	.16	Trace. Trace.	+++	88.6	6.1	3.6	1.1	.6	.....
April 17.....	1017 1400	9.18	17.02 8.09	.72 .59	.79 .29	.30 .10	.20	Trace. Trace.	Trace.	87.2	6.4	3.2	1.1	2.1	.....
April 18.....	1017 950	9.77	17.65 8.25	.69 .57	.82 .30	.35 .12	.53	Trace. 0	0	84.4	5.8	3.1	1.2	5.5	.....
April 19.....	1020 1320	10.49	19.26 9.00	1.10 .90	.87 .32	.34 .11	.16	Trace. 0	0	85.8	8.6	3.1	1.1	1.4	.....

* + Ammonia—N.

Date.	Sp. Gr. Volume in c.c.	Total Nitrogen, gm.	Urea, gm. Urea —N.	Ammonia, gm. Ammonia —N.	Kreatinin, gm. Kreatinin —N.	Uric Acid, gm. Uric Acid —N.	Undetermined —N.	Acetone. Diacetic Acid.	Indican.	In Per Cent. of Total Nitrogen					Diet. Purin-free and Kreatin-free.
										Urea.	Ammonia.	Kreatinin.	Uric Acid.	Undetermined —N.	
April 20	1023 1140	12.92	24.57 11.48	.68 .56	.86 .32	.57 .19	.47	0 0	0	88.2	4.3	2.4	1.5	3.6	+280 gm. beef.
April 21	1027 1000	15.12	26.58 12.42	.71 .58	1.01 .38	.90 .30	1.44	0 0	0	82.2	3.9	2.5	2.0	9.4	+300 gm. beef.
April 22	1016 1000	10.62	19.16 8.95	.87 .72	.95 .35	.49 .16	.44	0 0	+	84.3	6.8	3.3	1.6	4.0	.....
April 23	1020 770	8.82	16.47 7.70	.64 .52	.83 .31	.51 .17	.12	0 0	Trace.	87.3	5.9	3.5	1.9	1.4	.....
April 24	1016 1210	10.69	20.59 9.62	.72 .59	.86 .32	.48 .16	.00	Trace. 0	+	90.0	5.5	3.0	1.5	0.0	.....
April 25	1016 1350	10.97	21.03 9.83	.87 .71	.87 .32	.30 .10	.01	0 0	+	89.6	6.5	2.9	0.9	0.1	.....
April 26	1015 1270	9.88	18.67 8.72	.72 .59	.82 .31	.43 .14	.12	0 0	Trace.	88.3	6.0	3.1	1.5	1.1	.....
April 27	1018 1050	11.79	22.33 10.44	.87 .71	.83 .31	.54 .18	.15	0 0	+++	88.5	6.0	2.6	1.5	1.4	.....
April 28	1020 770	9.72	17.81 8.32	.81 .67	.86 .32	.37 .12	.29	0 0	+	85.6	6.9	3.3	1.3	2.9	.....
April 29	1027 590	7.58	13.60 6.35	.77 .63	.72 .27	.54 .18	.15	++ ++	++++	83.9	8.3	3.6	2.4	1.8	Attack.
April 30	1016 860	9.37	16.57 7.74	.93 .77	.77 .29	.68 .23	.34	+ 0	+	82.7	8.2	3.1	2.4	3.6	Attack.
May 1	1021 850	11.50	21.54 9.60	.85 .70	1.06 .39	.95 .32	.49	0 0	+++	83.4	6.1	3.4	2.8	4.3	.....
May 2	1018 1020	9.78	18.46 8.63	.68 .56	.72 .27	.48 .16	.16	Trace. 0	+++	88.2	5.7	2.7	1.6	1.8	.....
May 3	1016 1740	11.75	22.33 10.44	.84 .69	.88 .33	.38 .13	.16	Trace. 0	++	88.8	5.9	2.8	1.1	1.4	.....
May 4	1023 780	9.58	17.79 8.32	.75 .62	.79 .29	.50 .17	.18	0 0	+	86.8	6.4	3.1	1.7	2.0	.....

was made April 20 and 21, by the addition of scraped beef to her diet, 580 gm. being eaten during the two days.[6] The excretion of both the uric acid, and the kreatin as kreatinin, was prompt and complete. The beef fed represented 1.05 gm. purin nitrogen. According to Burrian and Schur,[7] 50 per cent. of this should appear in the urine. Taking the average of the three previous days, the extra uric-acid nitrogen eliminated was 0.82 gm.; calculating from the three subsequent days, 0.56 gm.; therefore in either case above the normal figure. Tolerance for larger amounts of purin was not tested. This patient, therefore, whose uric-acid metabolism closely approached what von Noorden[8] considers characteristic of the gouty, uric-acid retention, alternating with increased excretion, which is marked during the acute attacks, nevertheless showed a tolerance for considerable amounts of exogenous purins; an example of the complexity which the purin metabolism exhibits.

We regret that it was impossible to follow the purin bases, since Mandel[9] has reported a very interesting parallelism between them and the temperature in aseptic wound fever. In his cases the uric acid exhibited an inverse relation, declining sharply during the fever, the opposite of its behavior in our case. Increase of uric acid following artificial fever has been observed by Linser and Schmid.[10]

The kreatinin elimination, between the paroxysms, showed the same constancy and independence of the total nitrogen elimination which, since the work of Folin,[11] and of Van Hoogenhuyze and Verploegh,[12] we have learned is characteristic of it. The daily quantity excreted was a little below the figure given by Folin[11] for moderately corpulent persons, 20 mg. per kilo, but corresponded with Closson's[13] lower figure of 17 mg.

The only variations from this normal level were produced by the attacks, and by the ingestion of meat, April 20 and 21. It is of interest to note that the increase in kreatinin output during the two attacks and after 580 gm. of beef was nearly identical. As the loss of weight during an attack was about 2 kilos, and of nitrogen 9 or 10 gm., it seems probable that this increase in urinary kreatinin was due to destruction of muscle

6. von Noorden and Schliep: Berl. klin. Wchnschr., 1905, 1297.
7. Burrian and Schur: Ztsch. f. physiol. Chem., 1897, xxxii, 55.
8. von Noorden: Handbuch der Pathologie des Stoffwechsels, ed. 2, ii, 161.
9. Mandel, Arthur R.: Am. Jour. Physiol., 1904, vii, 452.
10. Linser and Schmid: Deutsch. Arch. f. klin. Med., 1904, lxxix, p. 514.
11. Folin, O.: Am. Jour. Physiol., 1905, xiii, 84; Hammersten's Festschrift, 1906, Article 3; Upsala Läkaref. Förh., 1906, xi, Supplement.
12. Van Hoogenhuyze and Verploegh: Ztschr. f. physiol. Chem., 1905, xlvi, 415.
13. Closson, O. E.: Am. Jour. Physiol., 1906, xvi, 254.

tissue during the attack. The rather close correspondence of the uric-acid rise, seems to us a further argument for this view. That kreatinin elimination increases during fever, has, of course, been long known.[14] This seems to be the only clearly demonstrated exception to the rule that the endogenous kreatinin excretion is a constant for each individual.

The results of our study of the metabolism in this patient, while of interest from a theoretical standpoint, have shed no light on the actual causation of her attacks. The only careful study of the metabolism during recurrent vomiting is that of Howland and Richards.[15] Their findings for uric acid correspond exactly with ours, namely, a marked rise following the attack, with subsequent fall to normal. They were unable to make any observations in the period preceding an attack. They interpret their figures, however, as evidence of diminished oxidation of uric acid, and adduce figures for the sulphur metabolism in support of this. On this they build a theory of diminished activity of the oxidizing ferments as the primary cause of the sydrome of recurrent vomiting, acting through an increase in the toxicity of such substances as indol. For this they offer experimental proof that the toxicity of indol increases greatly when administered to dogs poisoned with potassium cyanid, which diminishes oxidation.

The combination, in our case, of increased uric acid and kreatinin elimination, and nitrogen and weight loss, points rather more strongly to increased oxidation. It is unfortunate, in both cases, that accurate determinations of the purin bases were not made, since an increased conversion of these into uric acid would equally explain increased excretion of the latter.

It seems to us most desirable that cases of recurrent vomiting and other probable metabolic disorders, as well as the shorter fevers, should be subjected to careful chemical investigation on standard diets of different types, with reference to the special endogenous metabolism. Most of such work in the past has considered only the nitrogen and energy balances.

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14. von Noorden: Handbuch der Pathologie des Stoffwechels, i, 599.
15. Howland and Richards: Arch. Pediat., 1907, xxiv, 401.

INFECTION OF MAN BY DIPTEROUS LARVÆ.

WITH REPORT OF FOUR CASES.*

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The presence of various fly-larvæ as parasites or as pseudo-parasites of man has attracted little attention, although it has been noted since very early times and is of constant, although relatively infrequent, occurrence.

Homer mentions a maggot affecting man. Plutarch tells of Mithridates being condemned by Artaxerxes Longimanus to be devoured by fly-larvæ. He was left bound, with his face smeared with honey, and fed daily. When he died on the seventeenth day it was found that the fly-larvæ had so consumed his flesh that his entrails were exposed and covered with the larvæ. Herod Agrippa also was "eaten of worms and died." Later we find Galen prescribing a remedy for ulcers inhabited by "worms."

During the sixteenth and seventeenth centuries especially do we find a great many records of fly-larvæ as well as more remarkable creatures that were found in the feces, vomitus and urine of patients. Many of these were doubtless more or less fanciful and, as is occasionally the case to-day, the reports of hysterical patients.

Authentic cases are numerous, however, not only of infection by fly-larvæ, but by other insect larvæ as well. Hope[5] records a cause of a boy that vomited large numbers of the English cabbage butterfly, and Hope, Chichester,[4] Pickels,[17] Sandberg[21] and Blanchard[2] report cases of infection with beetle larvæ. Other cases are given by Kirby and Spence,[8] and Hope gives a table of reported cases. Such cases are, however, rare and accidental, but in the case of certain few dipterous larvæ we are concerned with species whose normal mode of life is parasitic or with species that readily adapt themselves to parasitic existence.

Infection by fly-larvæ was designated by Hope as myiasis and has been divided by other authors (Joseph) into myiasis externa or dermatosa and myiasis interna or intestinalis.

I shall take the infections by these larvæ up in their natural order. The nomenclature in each case is that of the original reporter.

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*From the Pathological Department of Northwestern University Medical School.

FAMILY SYRPHIDÆ.

This is one of the largest groups of flies and comprises those more commonly found about plants and flowers. But few cases are recorded of infection by larvæ of this family and these all by larvæ of the genus *Eristalis,* which are found in decaying vegetables and fruits and in decaying organic matter of all kinds or in water saturated with organic remains.

The following species are reported to have been passed from the bowels, but no definite history of the manner of infection or of the duration of their parasitic existence is given:

Eristalis diminiatus.
Eristalis tenax.
Eristalis arbustorum.
Eristalis pendulus.

FAMILIES SEPSIDÆ AND DROSOPHILIDÆ.

The larvæ of these two families are found in the leaves and stems of plants or decaying vegetables and animal matter. Some of the larvæ are aquatic.

The larvæ of *Piophila casei* are well known as the "skippers" of cheese and bacon. The eggs of this fly have been swallowed with cheese or bacon and have lived and developed in the human stomach and intestines until nearly ready to pass into the pupal stage (Meschede[12] and Moniez[13]). Infections by these larvæ were observed during the eighteenth century by von Rolander and Linné.

The larvæ of *Drosophila melonogastra* occur in fermenting fruits, preserves, vegetables, sour cream, etc., and are mentioned by Joseph[6] as occasionally found in the stomach and intestines.

The symptoms in both of these cases are those of acute gastric irritation and are discussed under the symptoms of myiasis intestinalis produced by *Anthomiidæ.*

FAMILY ANTHOMIID.E.

This comprises a family of flies "similar in appearance to the common house-fly, the main vein posterior to the middle of the wing turned upward. Eyes of the males large and contiguous, bristles of antennæ either feathery or bare" (Sharpe [22]). These flies are small or of moderate size and usually non-metallic in color. They are common about vegetable gardens and orchards and about heaps of decaying vegetable matter, compost and the like. One fly of the group is so common a frequenter of privy vaults as to have gained in Europe the name of the "privy-fly" and to have led to the supposition that the intestinal infection

was from eggs deposited on the anus (Finlayson[28]). These flies are frequently found about the house also and have been referred to as the "lesser house-fly."

The larvæ are characteristic in appearance; of an elongated conical shape, pointed anteriorly and more rounded posteriorly, showing their segments plainly, and bearing on each segment a pair of branched lateral branchiæ which are very prominent and replace the spiracles found in other groups of dipterous larvæ, enabling the animals to exist indefinitely in liquid and semi-liquid media.

The larvæ of the species which cause intestinal myiasis are found in vegetables, such as turnips, lettuce, beets, radishes, etc., in orchard fruits, and often occasion considerable loss to the gardner. Others live only in decaying vegetables and fruits and experiments on decayed fruit (Walsh[47]) have produced several varieties of fly larvæ from eggs previously deposited on the ripe fruit. Other flies of the group are parasitic on other insects as the locust, and another form was found in a tumor on the wing of a woodpecker. Kuchenmeister[7] and Wernicke state that anthomiid larvæ occur in the intestines of dogs and Iliff[24] reports an instance of the larvæ being found in the feces of a boa-constrictor.

The following species have been found parasitic in man:

Hydrotæa meteoricis.
Homolomyia cunicularis.
Homolomyia scalaris.
Anthomyia cunicularis.
Anthomyia furcata.
Anthomyia brassicæ.
Anthomyia saltatrix.
Anthomyia radicii.
Anthomyia ceparium.
Anthomyia fluvialis.
Anthomyia incisurata.

The larvæ of this family can live as true parasites of man for the full term of their larval existence, there seems to be little doubt. As will be brought out later, they do not, as a rule, have the digestive juices or the peristalsis of a normal intestinal tract to contend with. Their lateral branchiæ allow them to live in a fluid media and to draw their supply of oxygen from a considerable area; their inactive existence renders their need of oxygen very small. Hofman[23] points to the power of the larvæ to live in acid media (vinegar) as indicative of their ability to resist the acidity of the stomach. In the gastrointestinal tract they have presented to them also food which differs but little from the normal. From the length of time which the symptoms last in the different cases before the

larvæ are expelled and from the lapse of time between the history of ingestion of the probable source of infection and the appearance of the larvæ in the stools, it is to be assumed that the full period of larval life is passed in the intestine. It is, of course, evident that only the eggs or the freshly hatched larvæ could escape detection in the food or survive the masticatory process. In the case cited by Lampa[9] the larvæ went into the pupil stage almost immediately after they were expelled in the feces.

For the history of the following case I am indebted to Dr. Blankenmeyer, bacteriologist for the Illinois State Board of Health, at Springfield:

The patient was a man aged 30; weight, 145 pounds; rural mail carrier. For the last twelve years there had been constant gastrointestinal symptoms, abdominal pain, constipation and headache. On Saturday, May 19, 1906, the patient began eating raw pumpkin seeds and continued the same without other food until Tuesday morning; then a full dose of laxative mineral water was given. At noon of that day he passed from one thousand to one thousand five hundred larvæ, which proved to be a species of *Anthomyia*. The patient was put on calomel, santonin and aspidium but without further result. The abdomen decreased five inches in circumference and the patient professed to have slept better than for months previously.

In addition to the preceding instance I have collected reports of twenty cases. In nine of the twenty-one cases available there had been previous gastric disturbances or a lowered general resistance. Hofman[31] and Lublinski[46] diagnosed a previous gastric catarrh, Lublinski[46] gastroptosis, Huber[32] phthisis, and in other cases (as in that reported now) the history indicates gastric or enteric derangement. It is regretable that accurate gastric analyses have not been made so that it might have been learned whether or not the eggs and larvæ were subjected to the action of a normal gastric juice.

The onset is generally sudden and the symptoms those of an acute catarrhal gastritis and enteritis, but it may be more gradual, the symptoms merging with those of an antecedent gastric or enteric disorder.

General malaise and weakness are prominent; the face is pale and there is a complete loss of appetite. Nausea and vomiting occur at the onset and during the course; in some cases the larvæ are found in the vomitus. In many cases the gastric and abdominal pain is mentioned as severe; the pains are described by Lublinski as *"fürchterliche Leibschmerzen."* There is a feeling of distention and distress and in the classical case of Jenyus[36] a "tremulous motion" was complained of; in the case of Lockwood[43] there was "a choking sensation, as of worms crawling up the throat." All the remaining symptoms of acute catarrhal

gastritis are present, such as a coated tongue, acid eructations, mucus in the vomitus, excessive thirst and colicky pains. In the two cases recorded by Leidy[42] the symptoms are described as those of cholera morbus.

The nervous symptoms are especially prominent and severe; dizziness and violent headache occur, and in the case of Judd, the patient, a lad of fourteen, had violent spasms which disappeared with the passage of the larvæ. Krause[40] and Germar's[30] cases were characterized by severe epileptiform attacks. In both cases the attacks ceased with the passage of the larvæ. The patients were adults.

The larvæ have been found also in other parts of the body. Fairmaire[27] reports an ear infection in which anthomiid larvæ were found, and James[35] quotes an instance of nymphomania described by Wernicke, of Buenos Aires, with severe excoriations of the vagina and discharge, irrigation bringing to light anthomiid larvæ, which, so it was thought, "had developed in the rectal pouch and migrated through the parietes."

The diagnosis can be made only by finding the larvæ in the stools or vomitus. The prognosis is certain. The larvæ are passed out naturally within a time varying from one to fourteen days if no treatment is given, and with their passage the symptoms cease. Schlesinger[113] reports a fatal case of infection by fly-larvæ, in which the nature of the larvæ was not determined, but the result of the autopsy by Weichselbaum would seem to indicate that it was not an anthomiid infection.

The treatment in the published cases has varied. Lampa[9] is of the opinion that it is impossible to reach the larvæ by any means and that they will pass out in their own time, which is just before they enter into the pupal stage. Blanchard[1] also found all vermifuges and anthelmintics without effect; Meschede alone obtained good results from santonin. On the other hand, simple purgatives and laxatives have given good results. Finlayson[28] succeeded with a large dose of mineral water after aloin had failed; in other cases also a laxative water has freed the intestine of the parasites. It is likely from the structure of the larvæ that such would be the case, as they are possessed of no means of obtaining a firm hold on the mucosa and would be readily washed out by copious doses of laxative water or saline cathartics.

FAMILY OESTRIDÆ.

"Rather large or very large flies, with extremely short antennæ, having a segmented arista; the front of the head prominent; the posterior portion of the wings rough and with few veins; mouth usually atrophied, the trophæ being represented by tubercles" (Sharpe).

This is a small group of flies, of less than eighty species, the larvæ of all of which are true parasites in mammals; in birds and reptiles (terrapin) also, cases are reported (Leidy). The adult flies are well known as bot-flies, breeze-flies, warbles, heel-flies or gad-flies, and present a very characteristic appearance. They are large, the common species hairy, with short antennæ and small eyes. The mouth parts are atrophied and the fly subserves only a generative function.

The larvæ are parasitic in various animals, as in cattle, horses, sheep, deer, rabbits, squirrels, etc., and are found in various parts of the body; beneath the skin in cattle (*Hypoderma*), in the stomach in the horse (*Gastrophilus*), in the nasal sinuses of sheep (*Oestrus ovis*), beneath the skin and the scrotum of the squirrel (*Cuterebra cuniculi*), etc.

Gastrophilus equi.—The eggs of this species are deposited on the hair of the fore parts of the horse. The moisture and friction of the horse licking these parts opens the operculum at the free end of the egg, and the living larvæ are transferred to the horse's tongue. Osborne[52] has shown that this occurs most readily from the fourteenth to twenty-eighth day. The larvæ grow rapidly in the mucous secretions of the mouth and pharynx and are gradually passed on to the stomach, where they become fastened to the wall by the two chitinous oral hooks and grow rapidly. They are most abundant about the pyloric end. The larvæ remain attached to the wall of the stomach from late summer or fall until the succeeding spring, when they are passed out by the intestine and burrow into the ground, emerging as the adult fly in five weeks. The adult larvæ is three-fourths to one inch in length and elongated oval in shape. The head is slender and surmounted by two chitinous spines, below which is a double row of short, minute spines. Along the anterior margin of the first seven segments is a double row of short chitinous spines. Along the anterior margin of the eighth segment is a single row.

Raillet shows that these larvæ can exist in other animals, as in the dog. I have been able to find but two definite instances reported in man, although certain doubtful cases from their chronic nature and their severity would seem to belong to this class.

French[61] gives the case of a boy ten years old, who had been the subject of epileptic seizures for four years. When a free catharsis was produced larvæ were found in the stools which were said by Howard and Coquillet to belong to a species of *Gastrophilus*. But one more spasm occurred after the administration of an anthelmintic.

Schock's[88] case occurred in a woman with a chronic gastric catarrh.

Larva Migrans (Crocker).—There has been described by Hamburger[65] in this country, by Lee[73] in England, and by several Russian observers, Samson-Himmelstjerna,[84] Sokolow and others, an eruption which is supposed to be due to a species of *Gastrophilus,* possibly *hemorrhoidalis* or *pecorum.* The etiology is not certain, however, and Newman (Galloway[62]) supposes it to be due to some acarine mite, possibly *Tetranychus telarus.* It starts an itching pimple or small fissure and proceeds as an irregular, unbranched line, red, slightly raised, 2 mm. wide, and just beneath the skin. The parasite is found about 0.5 cm. beyond the reddened extremity of the line, and can be seen with a lens by rendering the skin just beyond the line anemic by pressure with a glass slide, when it appears as a black speck 0.5 to 1 mm. long. It moves about the body in a very irregular manner, advancing from 1 to 15 cm. per day, and is accompanied by severe itching and discomfort. The part previously traversed heals rapidly, leaving for a while a pigmented line.

It especially affects children and young peasants working in the fields. Only the uncovered parts of the body are attacked. So far it has been observed principally in Russia.

Genus Hypoderma.—The larvæ of species of this genus are normally parasitic beneath the skin of cattle, and of buffalo, deer, camels, etc. In this country two species have been described—*Hypoderma lineata* and *Hypoderma bovis.* Of these, *Hypoderma lineata* is found universally in North America and it seems probable that the cases of infection by *Hypoderma bovis,* which is the common old-world species, should be referred to *Hypoderma lineata.*

Hypoderma lineata is found in all portions of the United States, but especially in the south and middle west. The adult fly is found in the open fields, rarely in wooded places or in the stables, and it rarely follows the cattle into the water. The eggs are deposited generally in the late summer or early fall, on the heels and hind parts of the cattle, fastened four or six together on a hair, one fly often depositing a very large number on each animal. It was long supposed that the larvæ hatched from these eggs burrowed at once beneath the skin, thus finding their way to the back and shoulders. It was also thought by some that the fly in the act of deposition placed the eggs beneath the skin, a painful process which would explain the great terror which the cattle are said to have of these flies. Cooper Curtice[56, 57] has shown, however, that here, as in the case of *Gastrophilus equi,* the larvæ are licked off by the animal, thus finding their way into the pharynx and esophagus. The larva as found in the esophagus when first hatched is about 0.08 mm. long by 0.02

mm. wide and of a slender, elongated oval in shape. It is densely covered with spines, those on the terminal segment being much larger and curved backward. Two oral hooks are present on the first segment.

In the second stage, which represents that most commonly found in the pharynx and esophagus and which is the form first found beneath the skin, the larva is from 11 to 14 mm. long and has lost all except a few short spines about the anal spiracles and the mouth parts. In this stage it lives in the secretions of the pharynx and esophagus for several months, generally migrating through the cellular tissues to just beneath the skin about December.

The parasite found beneath the skin at first is identical in form with that found in the esophagus. The larva migrates around in an irregular manner, living on the wound secretions, and grows rapidly, so that it causes a palpable tumor.

In the third stage the larva is about 16 mm. long, is broader and tapers anteroposteriorly. The spines are again prominent, but they are differently arranged and are not as prominent as in the adult larva. The tubercles have not yet developed.

In the fourth stage it is about 22 mm. long and is a thick, fleshy grub, grayish white in color, sometimes showing a brown color in the later stages. The spines are larger, less numerous and thick tubercles are developed on the segments. In this stage the larva burrows through the skin and falls to the ground, ready to enter into the puparium.

These larvæ have been known as parasites of man for centuries. At one time an *Oestrus hominis* was described, but all such cases have been shown to fall within the well-known species parasitic in animals, in this country *Hypoderma lineata* and in Europe *Hypoderma diana*.

The following case was sent to Dr. Zeit by Dr. J. G. Holmes, of Fierro, New Mexico. I am indebted to Dr. Holmes for the history.

The patient was a boy, aged 13; goat-herder; no history of any previous gastric disturbance. In the fall of 1905, the patient began to complain of indigestior, regurgitaton of food, belching and gastric pain of irregular occurrence. The bowels were regular and the patient was apparently in other respects, well.

In November he noticed a swelling on the chest. It moved over the upper part of the body, head and arms, never staying in one place more than three or four days. Where the swelling had been a yellow stain was left which disappeared after several days. At one time the patient noticed two distinct swellings, one on the head and one on the shoulder. Occasionally he would apparently be free from the swellings and tender spots for two or three days.

The patient was examined by Dr. Holmes on several occasions. On the first examination in December the tender spots on the right side of the chest over third and fourth ribs, was slightly swollen, red, and about three or four inches in diameter, with no fluctuations, tender to touch, and often causing great pain. At another time the swelling was over the left ear, on the scalp.

On Dec. 30, 1905, the patient noticed a swelling on the right arm, painful

and red. During the day the swelling moved from the shoulder to the wrist of the same arm. On waking the next morning the swelling was on the anterior surface of the right shoulder over the head of the humerus, about two inches in diameter, red, and tender to the touch. A small circular hole about one-twentieth of an inch in diameter was noticeable at the center of the swelling. On the evening of December 31, while squeezing the swelling, the larva in question was expelled. It was about one-half an inch long. About one dram of thin, yellow serum followed. Recovery occurred after about two or three days. Subsequent health was good.

The larva in question was a larva of *Hypoderma lineata* in the second stage, or the first stage in which it is found beneath the skin.

There are several records of such cases in the literature, but none with a more complete history.

The persons most commonly affected are men whose occupation takes them about cattle or into the fields which cattle frequent. It is probable that some degree of personal uncleanliness plays a part and that the fly in depositing its eggs on man, if it does so, is guided by the odor of the cattle on the person in question. It seems more probable, however, from the fact that only one or very few larvæ are ever found in a single patient, that the living larvæ are transferred to the mouth.

The large proportion of children infected is especially noticeable. In seven American cases in which the larvæ were doubtless those of *Hypoderma lineata,* six were in children between the ages of six and twelve. The European cases, however, afford a larger proportion of adults.

The case above reported is the only one I have been able to find in which a definite history of gastric disturbance is given. From the life history of the worm we would expect a history of gastric pain.

The tumor usually appears during December or January and is first seen on the breast or on the neck. It is circumscribed, red, tender and moves about in an irregular manner, leaving a yellow pigmented trail, which gradually disappears. On palpation, movement may sometimes be detected within the tumor. Allen[50] closely observed the movements of the larva, marking with silver nitrate the spot where the larva was last seen. On one occasion it had moved only one inch, while at another time it traveled from the wrist to the elbow in twenty-four hours.

The presence of the larva occasions considerable burning and itching. Pain is present and is especially severe at night, keeping the patient awake.

If allowed to progress the tumor frequently becomes quiescent and a small opening is formed at its apex. The larva needs more oxygen for its now more rapid growth and the posterior end of the body, the posterior segment of which bears the principal breathing apparatus, is close below the opening.

The tumors may be found on almost any part of the body, but are usually on the upper trunk, neck, shoulder and arms. Hamilton gives a fatal case in which the larvæ were at the root of the tongue.

The treatment in each case is immediate excision of the larvæ.

Cephenomyia.—Several species of this genus are found parasitic in the nasal sinuses of sheep, in which they occasion very severe symptoms. Wesley Thompson reported a case in a man in San Bernardino, California. The patient, who had previously suffered from nasal catarrh, showed an accelerated pulse and fever, the nose was swollen and the nares nearly closed with dried blood and mucus. Forty larvæ were removed.

Dermatobia cyaniventris (Marquart, 1840), *Dermatobia noxialis* (Brauer, 1860), *Cuterebra noxialis* (Goudot, 1845).—I shall give these as one species, although Blanchard[21] distinguishes two separate species, *Dermatobia cyaniventris* and *Dermatobia noxialis.* Their classification and life-history are still indefinite and the cases in the literature are given as for a single species.

The larva is known and described under various local names, as the *ver macaque* (monkey-worm), *torcel,* and in Mexico *moyociul.* It is found in South and Central America and cases have been reported in the southern portion of the United States. It has so frequently affected man as to become known as the *Oestrus hominis,* under which title it has been frequently described in literature.

It attacks also horses, cattle, sheep, cats and dogs. It is probable that the eggs are deposited on the hair as in other species, although some observers describe a painful sting, on the site of which the tumor subsequently develops.

The tumor is found on all parts of the body, but especially on the buttocks. It is furuncular in appearance, motionless, and, according to most observers, very painful, although natives, who are frequently affected, are said to feel very little discomfort.

FAMILY SARCOPHAGIDÆ.

This family of flies is distinguished by "little more than that the bristle of the antennæ is feathery at the base, but hair-like and very fine at the tip" (Sharpe[22]).

The larvæ are found in decaying vegetable and animal matter, often in fresh meats and other foods. Several species are parasitic in other insects and others are parasitic occasionally in other animals and in man. The flies are exceedingly prolific and the eggs hatch very rapidly, or as in the genus *Sarcophaga,* the fly is viviparous or else the eggs hatch almost instantly.

Cases have been observed of intestinal myiasis in which species of *Sarcophagidæ* have been found (*S. hæmatodes, S. carnaria, S. hæmorrhoidalis, S. affinis.*

In man, however, the flies are most commonly found developing in suppurating wounds and ulcers and in chronic ear and nose affections, where there has previously been considerable discharge. In Egypt the larvæ have been found in ulcers beneath the eyelid.

Kohn[39] gives a case in which thousands of sarcophagid larvæ were found in the peritoneal cavity, whence they had found their way from an ulcus molle. Kirby and Spence[8] mention a beggar who was accus-tomed to placing his surplus contributions, especially meat, between his shirt and skin. Feeling ill, he lay down to sleep in the shade. What was probably a species of *Sarcophagidæ* consumed the meat and then attacked the man. When found he was too weak to help himself and the flesh was partly consumed from his breast so that he died in a hospital one hour after being moved there. Cloquet gives a similar case.

Larvæ of this family have also been found in furunculous swellings beneath the skin, in the vaginas of girls and women, especially where there had been a discharge. They are even reported to have penetrated the cranial cavity from infection of the sinuses or by the orbital fissure (Peiper[15]).

In Russia infections by these larvæ have been very frequent (Portschinsky[105]).

The following species have been found: *Sarcophaga carnaria, S. Magnifica, S. wohlfahrti, Sarcophila meigeni, S. latiferous, S. ruralis, S. ruficornis.*

FAMILY MUSCIDÆ.

The *Muscidæ* comprise our common house-flies, and are distinguished by the bristle of the antennæ being feathered. The larvæ are found in all manner of decomposing matter and are everywhere well known.

Several larvæ of *Musca domestica* were sent to Dr. Zeit, having been found in the stools of a patient and mistaken for *Distomes.* No history of any kind was obtainable.

Dr. Leidy[42] reported a case in which the larvæ of the bluebottle fly (*Lucilia cæsar*) had been found in the stools.

In the cases given by Krause[110] and Senator[114] a description of the symptoms is given. These are identical with those observed in other cases of intestinal myiasis.

Larvæ of *Muscidæ* have also been found in wounds and in ulcers, in the ear, nose and vagina.

A patient presented himself to Dr. Zeit, complaining of severe pain in one ear accompanied by some discharge. Several days previously one of the common species of flies had got into his ear and lodged in the canal, but after a moment or two it ceased to discomfort him and he supposed that it had escaped. On examination the remains of a fly were found in the canal, while the skin and the connective tissue over the cartilage were riddled with small burrows in which were numerous larvæ. These were removed by means of forceps and antiseptic washes. The species was not determined.

The following species of *Muscidæ* have been reported occurring in the intestine: *Musca pendula, Musca domestica, Musca stabulans, Calliphora vomitoria, Lucilia cæsar.*

The following species have been reported in wounds and in other external affections: *Musca domestica, Musca stabulans, Calliphora vomitoria, Calliphora erythocephalus, Lucilia cæsar.*

Compsomya (Lucilia) macellaria.—The screw-worm, the larva of *Compsomyia macellaria,* is by far the most frequent cause of myiasis externa in the United States and the one which causes the most serious consequences. It is found throughout the southern part of the United States, in Mexico, South and Central America. Occasionally a case of infection by the larva has been reported in the northern states.

The larva is about three-fourths of an inch long. Between each two of the segments is a row of bristles which cause it to resemble a screw. The larva is pointed anteriorly and the head bears two sharp, pointed, strong black hooks. It is found in fresh and decaying meats and in infected wounds in cattle, sheep and other domestic animals, occasionally in man.

In man it is found in wounds, ulcers, in the ear and especially in the nasal sinuses and the pharynx. It has even invaded the eye-ball. Several fatal cases are reported and some idea of the extremely destructive nature of the infection may be gathered from Snow's case in which he found, after death, the cervical vertebræ denuded of all tissue, the hyoid bone destroyed, and the nasal bones held only by the superficial fascia. The palate bone broke on the slightest pressure.

A large number of these larvæ are often found in a single infection; and as many as two or three hundred have been removed.

Ochromyia anthophaga (Blanchard).—The larva of this fly infects man in South Africa in about the same manner as the *Dermatobia* larva in South America. The fly belongs to the *Muscidæ.*

In conclusion, I wish to thank Professor Zeit for his kindly assistance and for the specimens and laboratory facilities placed at my disposal.

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THE URINARY FINDINGS IN A SERIES OF INFANTS SUFFERING FROM INTESTINAL INFECTION.*

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Concerning the condition of the kidneys in infants suffering from intestinal infection there has been a wide difference of opinion. In a careful review of the literature by Morse[1] in 1899 the conflicting views were graphically stated. Among those whose opinions are founded on large personal experience may be mentioned Kjellberg,[2] who in 1870 found nephritis on autopsy in 67 out of 143 infants dying of acute or chronic enteritis. In 3 non-fatal and 15 fatal cases of the same kind the urine contained albumin, casts and leucocytes. Holt, writing twenty years later in Keating's Cyclopædia,[3] asserts that, although cloudy swelling of the renal tubules is common in enteritis as in other febrile diseases, true nephritis is uncommon, and that albumin in large amount, renal epithelium, and casts are exceedingly rare. Nevertheless, Czerny and Moser[4] in 1894 found nephritis in 11 fatal cases of gastroenteritis in infants under two weeks old. The frequency of nephritis, they admit, diminishes with age. In the same year Falsenthal and Bernhard[5] reported a series of 15 autopsies in cases of vomiting and diarrhea in which the urinary findings had been repeatedly studied during life. Marked degeneration of the convoluted tubules was demonstrated. The collecting tubules contained many casts and often blood. In the urinary examination albumin was usually present and often necrotic cells, casts of various kinds and leucocytes were found.

Morse[6] presents a series of cases all in infants attending the outpatient department ill with uncomplicated diarrheal diseases in which the urine was collected by catheterization and carefully examined. The

* From the Laboratory of the Thomas Wilson Sanitarium.

1. Morse: The Renal Complications of the Acute Enteric Diseases of Infancy, Arch. Pediat., 1899, xvi, 649.
2. Kjellberg: Jour. f. Kinderkr., 1870, liv, 192.
3. Holt: Keating's Cyclopedia, 1890.
4. Czerny and Moser: Jahrb. f. Kinderh., 1894, new series, xxxviii, 430.
5. Felsenthal and Bernhard: Arch. f. Kinderh., 1894, xvii, 222.

clinical diagnosis was fermental diarrhea in 64 instances and ileocolitis in 6. Albuminuria due to renal complication was noted in but 10 cases, 14 per cent., and, except in one instance, was of small amount. Casts were found in but 6 of these cases. No mention is made in this analysis of pus cells, although in the table pus is recorded as present in the sediment in 4 instances, and in 8 other cases an occasional small cell is noted. No relation was made out between the urinary condition and any of the symptoms, and Morse concludes that the renal changes in the acute diarrheas are usually moderate in degree and degenerative, and not inflammatory in character. It is unfortunate that, in each of the cases reported by Morse, but a single examination of the urine was possible and that many of the cases passed at once out of observation.

In the same year Koplik[6] reported a series of 25 infants and children with acute or subacute gastroenteritis, in which albumin alone was found in 4 instances, albumin and casts in 13, albumin with casts and pus twice, and casts alone once, while the urine was normal in but 4 cases. Although Koplik thinks that these findings justify the term nephritis, he recognizes that the condition, on account of its rapid improvement without renal lesion, is different from the nephritis in adults or that after scarlet fever. It is brought about, he suggests, by the action of toxins in concentrated form upon the kidneys, because of the great loss of fluid.

Recently Chapin[7] found albumin in 75 out of 86 cases of disturbance of the gastrointestinal tract, in 37 of which casts were also noted. These elements were present in a somewhat larger ratio in a series of pulmonary and general diseases. The almost uniform presence of albumin, often with a few casts in many febrile affections in infancy has been repeatedly noticed by Jacobi[8] and others. It seems, therefore, that although renal complications play a small rôle in gastroenteric affections of mild and moderate grade, yet in the severe forms they are more serious.

The present study was undertaken with the hope that a somewhat more extended analysis of the urinary findings in a series of infants suffering from diarrheal affections, and under constant observation in hospital wards, might indicate more clearly the extent and frequency of renal complications in intestinal diseases.

INTRODUCTORY STATEMENT.

The cases studied were those of 72 infants admitted to the wards of

6. Koplik: New York Med. Rec., 1899, lv, 451.
7. Chapin: Arch. Pediat., 1906, xxiii,, 329.
8. Jacobi: New York Med. Jour., 1888, xlvii, 225.

the Thomas Wilson Sanitarium.[9] They may be divided for our purposes into two groups—those with intestinal infection and those without. The urine was collected in specially arranged flasks or test tubes, or, in the case of girls, directly in a vessel or obtained by catheterization In many instances a number of specimens were obtained from the same case.

The first group, the diarrheal cases, consisted of 53 infants; of these 33 had dyspeptic or fundamental diarrhea of varying degrees of severity, and 20 ileocolitis, as determined chiefly by the character of the discharges. In many of the latter cases there was evidence of intestinal ulceration.

GENERAL CHARACTER OF THE URINE.

In 31 of these 53 cases no pathologic elements were found in the urine; in 22 instances the urine contained albumin, casts, pus, red blood corpuscles, or several of these elements together, as will be specifically stated later on.

AGE PERIOD.

The infants studied fell into the following age periods:

Birth to 3 months	5
4 to 6 months	14
7 to 9 months	17
10 to 12 months	5
13 to 24 months	12
	53

Thus more than half were in the middle half of the first year.

SEX.

But little interest attaches in this preliminary analysis to the sex of the cases studied. They were: Boys, 34; girls, 19. Total, 53.

DURATION OF ILLNESS.

The duration of illness at time of urinary examination may be briefly stated as follows in periods of weeks:

1 week or less	8
1 to 2 weeks	8
2 to 3 weeks	12
3 to 4 weeks	7
4 to 6 weeks	12
6 to 8 weeks	2
3 months	3
Uncertain	1
	53

9. Hospital for children suffering from intestinal disorders, situated in the country ten miles from Baltimore.

As the urine was usually examined shortly after admission, this date indicates that the babies when received were suffering from more than light transitory intestinal derangement. This is also shown by the result of treatment.

RESULT OF TREATMENT.

Discharged well	30	57 per cent.
Discharged improved	11	20 per cent.
Discharged unimproved	4	8 per cent.
Died	8	15 per cent.
	53	

This table indicates that the cases studied were of somewhat severer character than those of the sanitarium as a whole.

Passing from the more general consideration to a study of the cases in which the urine was abnormal, a further analysis should consider the extent and nature of the urinary alterations and the renal changes, if any, indicated thereby. Twenty-two cases were found. It has long been known that in any febrile or toxic disease, a certain amount of albumin and some casts may be found in the urine, not because of an inflammatory lesion in the kidneys, but due rather to a parenchymatous degenerative process or "cloudy swelling" which the kidneys show in common with the other organs of the body and which may be of mere transitory character.

CLOUDY SWELLING.

Of the 22 cases, in 2 the presence of albumin was the only abnormality, while in 5 others albumin and hyaline casts were noted together. The albumin was never present in large amount, and the condition of the patients not particularly serious, with the exception of one infant who died of ileocolitis, in whom the renal condition was comparatively unimportant. All these patients had more or less fever; one had convulsions.

PYELITIS.

We regarded the presence of pus, polymorphonuclear leucocytes, in fairly large numbers in the urine as significant of a definite inflammatory process in the urinary tract. There was no evidence in the whole series of any urethritis or cystitis. The region of the bladder was repeatedly palpated in all our cases, and in no instance was any tenderness elicited. No frequency of micturition was noted. Pyuria alone or with moderate albuminuria without other change suggests pyelitis, although the exact extent of the renal involvement is difficult to determine. Cases belonging to this group were as follows: With pus alone, 2; with pus and albumin, 5, making 7 in all.

NEPHRITIS OR PYELONEPHRITIS.

When pus cells, together with albumin and casts, were found, the diagnosis of nephritis was made, especially when red blood cells or many bacteria were also present. This group of cases is as follows:

Pus with albumin and casts	4
Pus with albumin and casts and many bacteria	2
Pus with albumin and casts and red blood cells	2
	8

The casts were for the most part hyaline in character, though pus casts and granular casts were frequently found, but never in large numbers.

In regard to the character of the intestinal condition, these cases are divided as follows:

Dyspeptic or fermental diarrhea	10
Ileocolitis	12

Dividing the cases with urinary changes into three groups, as above indicated: *a*, albuminuria with or without casts; *b*, pyelitis (pus cells without casts); *c*, nephritis or pyelonephritis (pus cells with albumin and casts), the relation of each of these to the intestinal condition may be indicated thus:

	Dyspeptic Diarrhea.	Ileocolitis.
Albuminuria	3	4
Pyelitis	3	4
Nephritis	4	4
	10	12

This table suggests the conclusion that urinary findings may be altered by the toxins or fever in dyspeptic diarrhea, as well as during an ileocolitis. This may be because in many of these cases the two conditions are not to be sharply distinguished. A further analysis of the cases in respect to the intensity of the renal changes as indicated by the amount of albumin and the number of pus cells and casts shows about as severe involvement in the infants with dyspeptic diarrhea as in those with ileocolitis.

In respect, however, to the whole number of cases examined, the less frequent finding of urinary changes in dyspeptic diarrhea is brought out by the following table:

	Total No. Cases.	Urinary Change		Normal Findings.	
		No. cases.	Per cent.	No. cases.	Per cent.
Dyspeptic diarrhea	33	10	30	23	70
Ileocolitis	20	12	60	8	40
	53	22		31	

An analysis of the cases with pathologic urine according to their age may be briefly indicated:

Age Period.	Total No.	Pathologic-Urine No. Cases.	Per cent.
0 to 3 months	5	1	20
4 to 6 months	14	7	50
7 to 9 months	17	10	58
10 to 12 months	5	1	20
12 months	12	3	25
	53	22	

The number is too small to warrant sweeping deductions, but the figures suggest that urinary changes in intestinal disease are more frequent during the middle of the first year than at other times.

A larger number of our 22 cases occurred in boys than in girls; the number of boys in the series being 16, or 73 per cent., against 6 girls, or 27 per cent. This furnishes ground for the probability that the urinary changes were not brought about from without through urethral infection.

The results of treatment of the 22 cases with pathologic urine are instructive and may be indicated as follows:

	No. Cases.	Per cent.
Well	9	41
Improved	7	32
Unimproved	2	9
Died	4	18
Total	22	100

The results of the remaining cases studied in which the urinary findings were normal were:

	No. Cases.	Per cent.
Well	21	68
Improved	4	13
Unimproved	2	6
Died	4	13
Total	31	100

Thus, as far as our experience goes, the general result of treatment of cases with normal urine was somewhat better than in those with altered urinary findings. Of the former group 25 out of 31, or 80 per cent., were bettered, while 6, or 20 per cent., were unimproved, whereas in the latter group of 22 cases, but 16, or 73 per cent., were bettered, and 6, or 27 per cent., were unimproved.

The result of the treatment is also instructive in relation to the form of intestinal derangement.

CASES WITH ABNORMAL URINE, 22 IN NUMBER.

	No. Cases.	Bettered.	Not Bettered.
Dyspeptic diarrhea	9	9	0
Ileocolitis	13	7	6
Total	22	16	6

CASES WITH NORMAL URINE, 31 IN NUMBER.

	No. Cases.	Bettered.	Not Bettered.
Dyspeptic diarrhea	23	22	1
Ileocolitis	8	3	5
Total	31	25	6

Our tables must not be taken as indicating the effect of urinary complications in cases of ileocolitis. Of the 13 patients with ileocolitis having some alteration in the urine, 7 were bettered and 6, or 46 per cent., were unimproved, while of the 8 babies suffering with ileocolitis in which the urine was normal, but 3 were improved, and 5, or 62 per cent., were not bettered. In certain instances to be cited the persistence of urinary complications in ileocolitis are clearly seen. In several of the cases in which the urinary findings were negative, more frequent examination of the urine might have disclosed a pathologic condition.

CASES OF URINARY ABNORMALTIES WHICH DID NOT HINDER RECOVERY.

In many instances the abnormal condition shown by the urine did not seem materially to affect the outcome. Of the latter class two cases may be cited:

CASE 1.—F. S,. Clin. No. 141, a child of 4 months, for the most part breast-fed; on admission had been ill for two weeks with vomiting and diarrhea. The stools were seven to eight a day and contained mucus and curds. There was no blood or pus in the discharge at any time. Repeated urinary examinations showed a small amount of albumin and a few hyaline casts with a considerable number of pus cells. The child vomited frequently on mother's milk. This was alternated with a low milk mixture to which sodium citrate was added. The stools quickly became normal in character, but remained five to six in twenty-four hours. The baby was discharged after three weeks apparently well, but with a trace of albumin and some pus cells still in the urine.

A somewhat similar case is the following:

CASE 2.—D. F., Clin. No. 229, a colored infant, aged 8 months. About the history little was known, except that the child had been "boarded out," fed on condensed milk and table diet and for the past two weeks had had vomiting and diarrhea with eight to ten mucous stools a day. After admission the number of stools was considerably reduced, but they still contained mucus. Several days later albumin and considerable pus were found in the urine, but no casts. The temperature arose to 103. The general condition of the child improved after this and the temperature became normal, but despite the liberal use of hexamethylenamin (urotropin) the pyuria persisted and was present on discharge, although the patient otherwise seemed well.

THE URINARY COMPLICATION AS THE CHIEF AILMENT.

In the next case the urinary condition probably indicated the chief ailment.

CASE 3.—V. B., Clin. No. 82, a child aged 1 year, had had vomiting and diarrhea occasionally for a month. The stools never contained blood, but were largely mucous and numbered ten to twelve daily. The temperature during the whole period of observation, about seven weeks, showed marked daily variations

similar to that in septic infections, sometimes reaching 105 F. Numerous râles were occasionally found in both lungs, but never any tubular breathing. Pyuria of a marked grade was present practically throughout. Only a small amount of albumin was discovered. Repeated cultures from the urine showed it to contain many colon bacilli. Variations in diet, irrigations and the persistent use of urotropin by mouth and rectum failed to affect the urinary condition. The child gradually lost weight, became peaked and emaciated, and died shortly after leaving the sanitarium.

NEPHRITIS AND PYELITIS.

In the two following cases of nephritis and pyelitis the urinary condition cleared up under observation.

CASE 4.—J. R., Clin. No. 107, a child of 6 months, admitted after an illness of about ten days in which the stools were frequent, mucous, and occasionally blood-tinged. There was some elevation of temperature and the signs of marked sepsis. The first examination of the urine showed a moderate amount of albumin, many hyaline casts, epithelial cells and many pus cells. Under a cereal diet, then one of diluted milk, and the use of hexamethylenamin, the condition of the urine gradually cleared and three weeks after admission was normal.

CASE 5.—A. S., Clin. No. 175, a child of 4 months, had been ill for three weeks with fever, vomiting and frequent mucous stools. There was no history of blood. When first seen the patient was drowsy and the heart action irregular. The urine contained albumin and hyaline casts and a considerable quantity of pus. The temperature was irregular and ranged from 97 to 103. On two occasions diacetic acid and acetone were present. Calomel and diet, first of cereal and then of diluted skimmed milk, were given, after which the general condition improved, the stools became fecal and the urine normal.

In none of the cases cited—indeed in none of the whole series—were there localizing symptoms, nor was any pain elicited in palpation over the region of the bladder; there was no increased frequency in micturition, and no urethritis; in short, the leucocytes and other abnormal features of the urine could hardly have been introduced from the lower urinary tract.

SOURCE OF INFECTION.

The source of infection in these cases is apparently the intestinal tract, particularly the lower bowel. The infection reaches the kidney either through blood or lymph stream, or by direct contact. At autopsy one frequently finds a thickened and ulcerated colon lying immediately on a kidney. In repeated bacteriologic examinations in several cases in this and in other series, the colon bacillus, the predominant inhabitant of the lower bowel, has been present in the cloudy urine.

As has been stated, among the 53 infants having intestinal disease, 8 died, 7 of ileocolitis, and 1 of dyspeptic diarrhea. In 4 fatal cases, all of ileocolitis, there were pathologic urinary findings. In the remaining patients who died, 3 of ileocolitis and 1 of dyspeptic diarrhea, the urine was normal.

CASES WITH AUTOPSIES.

Autopsies were performed in 5 instances; 2 in cases of ileocolitis with negative urinary findings, and 3 in cases also of ileocolitis, but with pathologic urine. A summary of the clinical histories of these cases with the autopsy findings is as follows.

CASE 1.—*Diagnosis.*—Ileocolitis (urine normal).

Patient.—I. S., aged 7 months, Clin. No. 215, admitted acutely toxic and hard to arouse. The onset of the illness occurred three days before with violent vomiting and purging. The temperature was markedly remittent. The stools were mucopurulent, definitely blood-stained. There was some tenesmus. The urine was normal. The child, after a short period of apparent improvement, died from toxemia.

Autopsy.—On section, moderate cloudy swelling of the liver and kidneys were found. The mucosa of the large bowel from valve to rectum was thickened with considerable superficial loss of substance. The peritoneal lymph glands were enlarged. Microscopic examination of sections of the kidney showed considerable swelling of the cells of the convoluted tubules. The nuclei stained rather poorly. The glomeruli and straight tubules appeared normal.

CASE 2.—*Diagnosis.*—Malnutrition, ileocolitis (urine normal).

Patient.—E. F., Clin. No. 245, an infant 6 months of age, weighing 9 pounds, was ill for a month with vomiting and diarrhea. Stools were watery, contained some mucus, but no blood. Under observation the child had no fever, but remained weak and listless and finally died of asthenia. The urine was negative.

Autopsy.—The heart was found to be somewhat enlarged and the mitral valve thickened. The mucosa of the lower ileum was swollen with numerous ulcerations of Peyer's patches in this reigion. The mesenteric and retroperitoneal lymph glands were hypertrophied. No abnormalities were noted in the other viscera. No section of the kidney was saved for microscopic study.

In the remaining fatal cases with autopsy the urine presented pathologic findings.

CASE 3.—*Diagnosis.*—Septicemia, albuminuria, fatty degeneration of kidney and liver.

Patient.—B. R., Clin. No. 174, aged 5 months, was admitted with a history of vomiting and diarrhea of a week's duration. The stools were not frequent, but were said to contain mucus and blood. The child was drowsy when first seen. There was a large fluctuating mass in the scalp at the occipital region, apparently a suppurating hematoma. The mother proved indifferent, and real abuse of the patient was suspected. Albumin in moderate amount was present in the urine. The child had an irregular temperature and died, apparently from a general infection, four days after admission.

Autopsy.—Little alteration was found in the intestinal tract except for a slight increase in the lymphoid tissue of the large intestine. The mesenteric and retrosternal lymph glands were enlarged and softened. The organs, particularly the liver and kidneys, indicated fatty degeneration. The cortex of the kidney was pale yellow in color. The striations and glomeruli were not well defined. The renal pelves and the ureters were normal. On microscopic examination the sections of the kidney were found to stain poorly; there was marked parenchymatous and fatty degeneration, particularly in the cells of the cortical area, and but little small cell infiltration. The liver cells were largely displaced by fat droplets, particularly in the center of the lobules.

In the above case the renal involvement and albuminuria were prob-

ably not due primarily to the intestinal condition, but to the general infection following the scalp lesion.

CASE 4.—*Diagnosis.*—Ileocolitis; nephritis.

Patient.—G. K., Clin. Nos. 246, 302, aged 7 months, had been ill when first seen for two months with mucopurulent, frequently blood-stained, stools. The child was markedly emaciated with scaphoid abdomen; otherwise the physical examination was negative. The urine contained albumin in considerable quantities, also hyaline and granular casts and pus cells. The patient was unusually lethargic, but seemed slowly improving when he was taken home against advice. He was returned a few days afterward much worse. The stools were all deeply blood-stained. He died in coma a few hours after his second admission.

Autopsy.—The absence of subcutaneous fat as well as the paleness of the musculature was a striking feature. There was marked chronic passive congestion of all the organs. The renal cortex was thickened and slightly granular. Several small uric acid calculi were present in the renal pelvis and ureters. The intestine showed the most pronounced changes; beginning midway in the ileum the mucosa was thickened and the seat of scattered punched-out ulcers increasing in number near the ileocecal valve. The large intestine to the rectum presented a swollen inflamed mucosa studded with numerous ulcers. The mucous membrane was in certain areas almost in shreds. The mesenteric glands were large and hyperemic. The urinary bladder was normal.

Microscopic Examination.—The sections of the kidney showed pronounced degenerative changes, limited largely to the cells of the convoluted tubules. In these the protoplasm stained poorly, was granular, and often contained numerous fat droplets. The nuclei were not stained with hematoxylin. In many instances the outlines of the cells were ragged and irregular. These changes were limited to the cells of the convoluted tabules. The glomeruli were little, if at all affected. The collecting tubules were normal. There was no accumulation of leucocytes or other evidence of inflammatory reaction.

CASE 5.—*Diagnosis.*—Ileocolitis, nephritis, pyelitis.

Patient.—E. B., Clin. No. 88, a baby of 10 months, had been seriously ill with mucous and bloody discharges for a month. On admission the intestinal condition seemed improved and the stools but little blood-stained. The child, however, was pale and weak, and had extensive thrush in its mouth, and excoriated buttocks. The urine contained large quantities of pus and some albumin. There was some suppression of urine. The patient became progressively worse and died in four days after admission.

Autopsy.—There was found some fatty degeneration and congestion of the liver and kidneys. In the renal pelvis the mucosa was the seat of numerous hemorrhages; the congestion and ecchymosis extended down both ureters to the bladder. The lining of the small intestine was normal to just above the ileocecal valve, where the mucous membrane became markedly swollen and beefy with many ulcers, small and also confluent. The mucosa of the large intestine was congested and ragged throughout. The lymphoid structures were everywhere enlarged. From bladder and renal pelvis pure cultures of colon bacilli were isolated. The sections of the kidneys on microscopic examination showed marked degenerative changes in the cells of the convoluted tubules. These stained darkly in eosin-like amyloid material. The borders of the tubules extending into the lumen were irregular and many of the nuclei stained feebly. There was no evidence of acute infection and no increase in connective tissue.

In these last two cases the urinary condition probably arose from direct infection of the kidneys from the overlying diseased bowel. From

the same source it is likely that constant reinfection occurred, and hence the pyuria persisted.

RESULT OF TREATMENT.

But little can be added from our experience to the treatment of cases in which there is abnormal urine. The nephritis as indicated by the amount of albumin and the number of casts is rarely of severe grade and tends to spontaneous improvement if the intestinal condition of the patient can be bettered. The diet was made as bland as possible, a cereal water was given with or without a small amount of egg albumin, and, as soon as it seemed safe, a milk mixture. In our hands a skimmed milk mixture was more easily borne than one containing more fat; although when the patient seemed able to digest fat it was given because of the desirability of reducing the proportion of proteid to fat and carbohydrate in the diet for a nephritic. When pyuria was the more prominent symptom, hexamethylenamin seemed of distinct value; of equal service were intestinal irrigations which emptied the lumen of the lower bowel of a certain amount of the infectious material.

THE URINE IN INFANTS HAVING NO INTESTINAL INFECTION.

For purposes of comparison the results of the examination of the urine in a number of cases which had no symptoms of intestinal infection are now indicated. These babies were suffering from the following ailments:

Malnutrition	6
Diarrhea, simple	6
Intestinal indigestion	4
Congenital heart disease	1
Diphtheria	1
Marasmus	1
Total	19

In the urine of none of these was any abnormality found. An analysis of these cases as in reference to sex and age may be briefly stated as follows:

Sex: Male, 13; female, 6. Total, 19.

Age period: 1 to 3 months, 2; 4 to 9 months, 9; 10 to 24 months, 5; 24 months and over, 3. Total, 19.

They differed from the infants already discussed in the fact that they gave no clinical evidence of gastrointestinal infection. As the nature of their disease suggests, they were not so acutely ill, although in some instances their ailments had been of long standing.

RESULTS IN THESE NINETEEN CASES.

All were discharged well except two, who died, one from congenital heart disease, and the other from marasmus.

To these cases may be added one, the exact nature of which was somewhat obscure.

Patient.—E. S., Clin. Nos. 105, 220, a child of 18 months, admitted with the history of having been ill for three months, in which time she had lost much weight. One week before admission there had been diarrhea, the stools containing mucus, "with some blood." On examination the child was found to be markedly emaciated with irregular heart action and respiration. The knee-jerks were much exaggerated and Kernig's sign was suggestive. The neck was slightly stiff and there was tonic contraction of hands and feet. There was evident mental impairment. The stools were normal after admission, and the patient improved on citrated milk. No lumbar puncture was made because of the rapid mending. The urine was found to contain a small amount of albumin, casts and some pus cells. The urinary findings persisted after the patient was discharged greatly improved. It was thought that this might have been a pseudomeningitis of intestinal origin, in which case the urinary condition was probably induced during the period when the mucus diarrhea was present. If so, the case belongs to the former group.

SUMMARY.

Urine of abnormal character was found in 22 out of 53 cases of intestinal infection in infancy.

Of these 22 cases the urine contained albumin and occasional hyaline casts as the only pathologic element in 7 instances, febrile or toxic albuminuria; in 7 others the presence of pus cells was the chief characteristic, pyuria (pyelitis); in the remaining 8 cases albumin casts and pus were all present, indicative of nephritis or pyelonephritis. The urinary changes were more frequent in ileocolitis than in dyspeptic or fermental diarrhea, though the extent of renal involvement seemed to depend less on the variety of the intestinal affection, and more on its intensity. The pyuria persisted in some instances without apparently interfering with convalescence; in others it yielded to urotropin and in still others it developed into a serious and fatal complication. The infection seemed to have its origin in the intestinal canal from whence it reached the kidney either through the blood or lymph streams or by contiguity of structure. There was no evidence in our cases of involvement of urethra or bladder or ascending infection.

The autopsies made, though few, indicated clearly that, although the kidneys frequently escape injury during enteritis, they become the seat of extensive secondary changes in this as in other forms of infection.

The renal changes during intestinal disease in infants seemed to be those of degeneration, parenchymatous, hyaline, and fatty of the convoluted tubules, rather than those of focal infection.

In a series of ailments other than intestinal infections, and for the most part less acute in character, no urinary abnormalties were discovered.

REPORT OF TEN CASES OF EPIDEMIC CEREBROSPINAL MENINGITIS TREATED WITH THE ANTIMENINGITIS SERUM.*

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On November 17, 1907, there was admitted to the Garfield Memorial Hospital a patient with epidemic cerebrospinal meningitis, who died seven days later. The occurrence of this case led us to secure Flexner's antimeningitis serum and to use it in the series presented in this report.

CASE 1.—*Patient.*—M. S., white, female, aged 18, was admitted to the hospital Nov. 25, 1907.

Onset of Present Illness.—Patient was taken sick November 20 with chill, pain in limbs and body, and headache. November 21 Dr. S. Logan Owens saw patient and found her in a stupor; temperature, 100; eyes, lungs and heart normal; constipated. November 23, roaring in head; pain chiefly confined to neck and right knee; vomiting; temperature 101, pulse 118. November 24 patient restless and noisy; Kernig's sign present; tache cérébrale present; rigidity of neck.

Physical Examination.—On admission to hospital, patient restless and noisy; there was rigidity of neck; limbs partially flexed on abdomen; hypersensitive; herpes labialis; slight mucopurulent discharge from eyes and nose; Kernig's sign marked; patellar reflex sluggish; Babinski's sign absent; tache cérébrale present. Lumbar puncture performed on November 26 and 15 c.c. of cloudy opalescent fluid obtained. Coverslips showed numerous polymorphonuclear leucocytes, a few mononuclear cells, and a few Gram negative diplococci, both extracellular and intracellular. Cultures positive, twenty-four hours later.

Clinical Course.—Between November 26 and 29 patient suffered intensely with pain in legs, back and neck and had to be kept under chloral and bromids. On the 29th another lumbar puncture was made and 46 c.c. of fluid withdrawn. This was not as cloudy as that of the 26th, and the number of leucocytes and diplococci was slightly diminished. Thirty cubic centimeters of the antiserum was injected through the puncturing needle. For the next forty-eight hours patient was delirious, restless and suffered a great deal with pain. Urine and feces involuntary. December 1, lumbar puncture: 38 c.c. fairly clear fluid withdrawn. Coverslips and cultures negative for diplococcus; 15 c.c. of serum injected. The right eye became intensely congested on the 29th. Lumbar punctures were made on the 3d, 5th, 7th and 9th; from 5 to 40 c.c. of fluid withdrawn, and 15 c.c. of the antiserum injected at each puncture. The diplococcus appeared in coverslips and culture in the fluid obtained on the 5th, and progressively increased in number. At the suggestion of Dr. Flexner, two injections each of 30 c.c. of the serum were made on the 11th and 12th. Fluid withdrawn on the 13th showed no diplococci, cultures were negative, and there

* Read before the Medical Society of the District of Columbia, May 20, 1908.

were practically no leucocytes. Punctures were made on the 16th and 23d and continued negative.

On December 10 patient developed a parotitis on the left side. Following the first serum injection, the temperature rose several degrees and continued irregular and high (99 to 103.8) until December 19, when it practically reached normal and remained so until her discharge from the hospital, Jan. 21, 1908. Patient had a complicated and tedious convalescence. On January 6 an iridectomy was performed on the right eye to relieve the tension by Dr. W. K. Butler. Patient had a severe arthritis of the right knee, a large bed-sore and a severe cystitis. Following the operation on the eye the patient made rapid progress and was discharged on January 21, recovered, the only sequela being the loss of the right eye.

Leucocyte Count.—On admission, 15,100; it rose several thousand following the serum injections, and was 15,600 on the 27th day of the disease. This latter count was probably influenced by the complicating conditions.

CASE 2.—*Patient.*—F. L., colored, male, aged 5 months, admitted to hospital Jan. 20, 1908.

Onset of Present Illness.—About forty-eight days previously child was taken sick with fever. Three or four days later became fretful, rolled his eyes about; there was twitching of hands and fingers and hypersensitiveness. About the second week head became retracted. About the third week patient began to vomit for the first time, and from then on lost flesh rapidly. Bowels were constipated. Child had a cough. Urine scant and sometimes not voided for three days (?). Patient was irritable and restless; probably had slight convulsions. (The foregoing account from the ignorant mother.) On January 10 patient was seen by Dr. Paul B. Johnson, who found: "Child moderately emaciated; abdomen sunken; skin wrinkled and thin; some enlargement of wrists and ankles; anterior fontanelle not closed and bulging—no pulsation; temperature 100, pulse 135, respiration 16; lungs and heart normal; abdomen negative; muscles of back and neck rigid; tenderness along spine; Kernig's sign absent." On January 14 a lumbar puncture was performed by Dr. Johnson and 10 c.c. of cloudy fluid obtained, showing Gram negative diplococci, intracellular and extracellular. January 15 and 16 there was marked coryza, which was improved on the 17th. Patient sent to the hospital on the 20th.

Physical Examination.—On admission to hospital: Much emaciated child. Marked rigidity of neck with opisthotonos. Babinski and Kernig sign absent. Tache cérébrale present. Slight cough with considerable nasal discharge. General hyperesthesia. Heart and lungs normal. Temperature 98.4, pulse 146, respiration 20.

Clinical Course.—Lumbar puncture performed January 21. Twenty c.c. of slightly cloudy fluid withdrawn. Coverslips showed numerous polynuclear cells and two organisms—a Gram negative diplococcus, extracellular and intracellular, and a Gram negative bacillus. The *Diplococcus intracellularis* and a bacillus of the influenza group were obtained in cultures, the bacillus growing only on blood-agar media. Another puncture twenty-four hours later gave 54 c.c. of fluid, more turbid than before, the same two organisms in larger numbers. Fifteen cubic centimeters of the antiserum was injected. Following the injection the temperature, which had risen to 100.8, dropped to normal, rose to 103 on the 26th, and was irregular and apparently unaffected by the subsequent injection and punctures. On January 24 an attempted puncture was unsuccessful. January 29 lumbar puncture was performed. Twenty-five cubic centimeters turbid, reddish-yellow fluid withdrawn, showing a larger number of polynuclear cells than before, but both organisms had completely disappeared—none could be found in coverslips and all cultures were negative. Fifteen cubic centimeters

of serum injected. This serum was given because of the turbid appearance of the fluid before bacteriologic examination, and was probably unnecessary. Another puncture was made on February 1, which showed the same number of leucocytes, but no organisms. The child died on February 2, the sixty-second day of the disease.

Autopsy.—This was limited to the brain and showed a marked hydrocephalus and meningeal lesions, principally confined to the base of the brain.

This being a case of chronic hydrocephalus at the time of admission to the hospital, as well as one of mixed infection, it was recognized as unsuitable for the serum therapy. The serum was given to observe its action on the organisms, and it is of interest to note that both disappeared from the spinal fluid following one injection of 15 c.c. This was further confirmed at the autopsy, at which coverslips and cultures from the brain were negative. Unfortunately no leucocyte counts were made in this case.

CASE 3.—*Patient.*—H. G., white, male, aged 4 years, admitted to hospital Feb. 19, 1908.

Onset of Present Illness.—Patient was in perfect health up to February 15, when he suddenly stopped playing and lay down. His hands became cold and he complained of headache and pain along his spine. Neck muscles became rigid and head retracted. No vomiting or convulsions. Pupils unequal, the right dilated, the left contracted. Strabismus, herpes labialis, involuntary urination, and Kernig's sign present, Babinski's sign not present. Patient very restless, conscious at all times. February 16 sent by Dr. Ramsburg to Children's Hospital, where a lumbar puncture was performed on the 18th. Twenty cubic centimeters of turbid fluid obtained which showed numerous polynuclear cells and Gram negative diplococci, extracellular and intracellular. Fifteen cubic centimeters of serum injected. Following the injection of the serum patient showed marked improvement. Transferred to the Garfield Hospital February 19.

Physical Examination.—On admission to hospital: Muscles of body rigid and head retracted. Strabismus, pupils unequal, herpes labialis, involuntary urination. Kernig's sign present, Babinski's absent. Patient talked intelligently. Temperature 101, pulse 128, respirations 32.

Clinical Course.—On February 21 a lumbar puncture was unsuccessful. On the 25th, the retraction of the head becoming greater, associated with a rise in temperature to 103.2, pain and restlessness, a lumbar puncture was performed; 15 c.c. of cloudy opalescent fluid withdrawn. Coverslips showed numerous polynuclear cells and a few Gram negative diplococci, extracellular and intracellular. Cultures were negative. Fifteen cubic centimeters of the serum was injected. Temperature fell to normal on the morning of the 27th. Meningeal symptoms disappeared within twenty-four hours after the injection, and patient made a rapid recovery, being discharged from the hospital March 6, 1908, without sequelæ. No leucocyte counts were made in this case.

CASE 4.—*Patient.*—M. H., white, female, aged 6, admitted to hospital March 13, 1908.

Onset of Present Illness.—Had measles and scarlet fever eighteen months ago. Mental condition not good following these diseases. Taken sick March 10 at 10 p. m., with headache and vomiting. Had five convulsions during the night. Seen by Dr. Owens at 5 a. m. March 11. Temperature, 101.6, with corresponding pulse and respiration; slight strabismus and general hyperesthesia; urine scanty and cloudy; constipated. On consultation later in the day with Dr. Owens a tentative diagnosis of epidemic meningitis was agreed on and removal to the Garfield Hospital advised. Patient did not reach the hospital until 8:30 p. m. March 13.

Physical Examination.—On admission to hospital patient semi-comatose and

extremely sensitive to touch and noise and Kernig's sign present; Babinski's sign absent; patellar reflex abolished. Tache cérébrale, strabismus, carphalogia, rigidity of neck, slight retraction of head. Temperature, 102.4 (rectal); pulse, 112; respirations, 36.

Clinical Course.—Lumbar puncture performed at 11 p. m., March 13. Thirty c.c. of turbid opalescent fluid withdrawn under moderate pressure. Coverslips showed numerous polynuclear cells and numerous Gram negative diplococci, intracellular and extracellular. Fifteen c.c. of the serum injected. The diplococcus positive in cultures. This child, barring an unfortunate deafness, which still exists, made a rapid recovery and left the hospital March 29. The temperature and meningeal symptoms reached normal and almost entirely disappeared by the seventh day after the serum injection. The probable cause of the deafness was a paralysis of the auditory nerve. The only time she complained of pain in the ears was on March 20 at 6 p. m., when there was pain in the right ear for a short while, but by midnight she was asleep without narcotics and she had no recurrence of pain in either ear subsequently.

Leucocyte Count.—Nine hours after admission, 30,800; three days later, 18,400; six days later, 15,200.

CASE 5.—*Patient.*—I. O., colored, male, aged 25, wall-scraper, admitted to hospital March 22, 1908.

Onset of Present Illness.—Beyond the fact that he had been "sick" for about a week before admission no history could be obtained.

Physical Examination.—On admission to hospital: Temperature, 101; pulse, 94; respiration, 36. Patient answered questions intelligently; pupils normal; no strabismus; Kernig's sign present; Babinski's sign absent; patellar reflex abolished; cervical muscles rigid; no retraction of head; consolidation of upper lobe of left lung; frequent cough and blood-tinged sputum (the latter showed pneumococci, but no tubercle bacilli).

Clinical Course.—Lumbar puncture was performed at 1 p. m. March 23. Thirty c.c. of yellowish-white turbid fluid obtained under moderate pressure. Coverslips showed abundant polynuclear cells and numerous Gram negative diplococci, intracellular and extracellular. Fifteen c.c. of the serum immediately injected. Diplococcus in cultures. March 25, muscular rigidity entirely disappeared. Good cerebration. Pulse poor quality. The temperature was but little affected by the serum injection, pursuing an irregular course until April 3, when from 101 it gradually fell to normal, reaching the latter on April 15. March 28 it rose to 102.8, with an increased leucocyte count. Lumbar puncture was again made on the 29th; 2 c.c. of clear fluid obtained, containing a few polynuclear leucocytes, but no diplococci. Five c.c. of the serum was injected. There was progressive improvement in symptoms following this last puncture and injection. The patient, however, had persistent and at times very severe headache, which did not disappear until April 14. He was also irrational during this period, singing a large part of the time. On April 23 he was transferred to the Washington Asylum Hospital in order that he might fully convalesce. At this time his temperature had been normal ten days and he had been sitting up in a chair for three or four days.[1]

Leucocyte Count.—Before the serum injection, 19,200; two days after the injection fell to 16,400; four days later rose to 21,200 (puncture and injection of the 5 c.c.). Following this it fell to 13,200 twenty-four hours later and went progressively down thereafter.

The last injection of 5 c.c. was probably unnecessary.

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1. This patient reported to us two months after discharge from hospital entirely recovered.

CASE 6.—*Patient.*—J. J., colored, male, aged 16, dairy hand, admitted to hospital March 25, 1908.

Onset of Present Illness.—Thirty-one days ago, after drinking considerable cream and milk, patient vomited and went to bed. No headache until two weeks ago and at this time had pain in back of neck and was sensitive to touch. Impossible to obtain any further history.

Physical Examination.—At hospital March 27: Head markedly retracted; extreme opisthotonos; responds intelligently to questions, but when left alone mutters a great deal; slight cough, no expectoration; Kernig's sign present; Babinski's absent; hypersensitive; chest negative. Temperature, 103; pulse, 104; respiration, 28.

Clinical Course.—Lumbar puncture was performed at 1 p. m. March 26. Thirty-five c.c. of slightly cloudy opalescent fluid obtained under moderate pressure. Coverslips showed numerous polynuclear cells and Gram negative bacilli with the morphology of the influenza bacillus. (The *Diplococcus intracellularis* was not observed at the time, though prolonged and careful search was made for the organism; several pairs were found later). Cultures were negative for the bacillus (plain as well as hemoglobin media), but gave several colonies of the diplococcus. March 28 pupils dilated and sluggish to light; condition otherwise the same. March 29, lumbar puncture again performed and 15 c.c. of the antiserum injected. The fluid obtained (12 c.c.) was more turbid than before, contained more polynuclear leucocytes, showed numerous diplococci and bacilli.

Following the serum injection the temperature dropped to normal within twenty-four hours, rose to 101.4 the second day, and fell to normal on the fifth day, where it remained until discharged, April 14. The retraction and opisthotonos entirely disappeared by the fifth day following the serum injection, though there was slight rigidity of the neck. Patient made an uneventful recovery and left the hospital without any sequelæ. This case is interesting in several respects: First, the duration of the disease before the serum was injected, thirty-four days; second, the rapid recovery and favorable effect of the serum injection on the extreme retraction and opisthotonos; and, third, the presence of a Gram negative bacillus in the spinal fluid in conjunction with the diplococcus. No punctures were made subsequent to the one injection of 15 c.c. of the serum.

Leucocyte Count.—On admission, 12,100; three days after serum injection, 13,600.

CASE 7.—*Patient.*—W. B., colored, male, aged 39, barber, admitted to hospital April 24, 1908.

Onset of Present Illness.—The only history obtainable was that three days before admission to hospital, patient was suddenly taken sick with chill, fever, headache and cough. (It was later learned that he had a bad alcoholic history.)

Physical Examination.—On admission to hospital patient stuporous. Rigidity of neck; Kernig's sign marked; Babinski's sign absent; patellar reflex exaggerated; chest and abdomen normal; temperature, 102.4; pulse, 96; respirations, 24.

Clinical Course.—A lumbar puncture was performed at 2 p. m. April 25. Seventy c.c. of turbid white fluid obtained under considerable pressure. Coverslips showed a few Gram negative diplococci, principally intracellular. Fifteen c.c. of serum injected. Temperature fell to normal the next morning and rose to 101.6 the morning of the 27th. April 27 patient answered questions intelligently. Patellar reflex absent. Pupils normal. Rigidity of neck still marked. No headache. Kernig's sign present. April 29, patient weaker; semi-stuporous; pulse rapid and only fair in quality; pupils normal; Kernig's sign and rigidity of neck unchanged. At 8 p. m. lumbar puncture made and 3.5 c.c. of turbid

yellowish white fluid obtained. (The needle probably was obstructed at this puncture.) Fifteen c.c. of serum injected. Coverslips showed very numerous organisms and a luxuriant growth was obtained in cultures.

April 30, neck very rigid and extreme pain on movement of head; patient stuporous; muscular twitchings and delirium; involuntary movements of bowels and urination. Patient improved in the evening and slept well during the night. May 1, mental condition slightly improved; rigidity still marked; Kernig's sign more pronounced; pupils responded but slightly to light. It was decided to inject two 30 c.c. doses of the serum on successive days as was done in Case 1. This was done on May 1 and 2, and the same result obtained—the organism entirely disappearing from the spinal fluid, both in coverslips and cultures, as determined by a puncture on May 9. The clinical condition, however, did not improve; in fact, grew worse. On May 3 the patient developed a pneumonia; died on May 14. Following the serum injection of 30 c.c. on May 2 there was a slight improvement in the clinical symptoms, which then grew worse. A lumbar puncture on May 9 gave a negative fluid, but 15 c.c. of the serum were injected. Another puncture on May 14 was also negative, no leucocytes even being found.

Autopsy.—Acute cerebrospinal leptomeningitis; small tumor in floor of left lateral ventricle in proximity to island of Reil; hypostatic pneumonia; fatty degeneration of myocardium; dilatation of heart; atheroma of aorta; fatty degeneration of liver and kidneys.

Leucocyte Count.—On admission, 22,900; fell to 18,100 two days after first serum injection; then rose to 24,600. Unaffected by the two 30 c.c. injections. On May 3 (development of the pneumonia) rose to 40,600. Fell to 17,700 May 6; rose to 31,200 on May 8, and then fell to 17,200 May 12.

Considering the evidences of toxemia shown at the autopsy, it is possible that if larger doses of the serum had been administered in the beginning the patient might have recovered, and we feel that this should have been done.

CASE 8.—*Patient.*—E. N., colored, male, aged 3, admitted to hospital May 14, 1908.

Onset of Present Illness.—Patient taken sick May 7 with fever and general muscular pain. May 11 there was slight stiffness of neck and partial Kernig's sign; mind clear. May 13, patient seen in consultation with Dr. Owens. At this time there was retraction of the head and Kernig's sign was positive. Patient admitted to the hospital 5 p. m., May 14.

Physical Examination.—On admission: Rational; head retracted; very restless; seemed to be in a great deal of pain. Kernig's sign only slight. Temperature 99.4, pulse 120, respirations 40. Patellar reflex normal. Babinski's sign absent.

Clinical Course.—Lumbar puncture made at 9 p. m., May 14. Fifty c.c. opalescent fluid obtained under moderate pressure. Coverslips showed Gram negative diplococci, chiefly intracellular. Fifteen c.c. of serum injected. May 16, child brighter and took nourishment well. Retraction of neck slightly improved; other meningeal symptoms about the same. Lumbar puncture at 3 p. m. One c.c. of fluid obtained which was quite clear. Coverslips showed a few polynuclear cells, for the most part degenerated. A few faintly stained diplococci were found. Cultures negative. No additional serum given. May 17, pupils normal and respond to light; no retraction of head, and postcervical rigidity less marked. Child perfectly rational. Kernig's sign very slightly positive. May 19, Kernig's sign absent. Child fretful; wanted to go home. Patient discharged May 25 recovered.

Leucocyte Count.—On admission was 30,800; twelve hours later 30,100; May 18, 17,100, and May 19, 12,800.

CASE 9.—Patient.—T. L., white, male, aged 17, patient of Dr. A. W. Boswell, admitted to Garfield Hospital Feb. 27, 1908.

Onset of Present Illness.—Patient taken sick February 22 with chill, vomiting, intense pain in back of head, general muscular soreness, when seen by Dr. Boswell in the morning. At 8 p. m. had a convulsion and became unconscious; had petechial rash, conjunctivæ injected; was restless. Pupils normal. Intense pain in back of head and near McBurney's point. Temperature 102, pulse 106, respirations 26. February 23, conditions about the same. Suppression of urine for twenty-four hours. February 27, case seen with Dr. George N. Acker and Dr. Davidson in consultation, showing the following condition:

Physical Examination.—Headache; pain in back and limbs; retraction of head; rigidity of spine; restless; delirious; herpes; localized abdominal pain; Kernig's sign present; Babinski's sign absent; patellar reflex absent. Patient transferred to the Garfield Hospital, where on admission his temperature was 101.8, pulse 94, respirations 24.

Clinical Course.—Lumbar punctures at 6 p. m. and at noon February 28 were unsuccessful. At 9:30 p. m. February 28 lumbar puncture gave 60 c.c. of slightly turbid opalescent fluid. Coverslips showed numerous polynuclear cells, but no organisms could be found. Cultures were negative. Another puncture on March 1, at which 30 c.c. of fluid were obtained, gave a negative result for organisms. Under the idea that the serum could not be given until the organism was found, this patient did not receive the serum until March 6, on which date a puncture showed the diplococcus in coverslips. He was given 25 c.c. This case was a very severe and protracted one, and for the sake of brevity only the general features will be given. The serum injection was not given until the fourteenth day of the disease, and in all 142.5 c.c. were given. Twelve lumbar punctures were made. Patient recovered without sequelæ on the thirty-fifth day. The temperature ran an irregular course until the twenty-fourth day, varying between 102 and 98; seemed unaffected by the serum injections. However, patient developed a parotitis, which went on to suppuration, and this may have been responsible for the elevation after March 9. The clinical symptoms were most severe. Patient comatose for days; very restless and had to be placed under a restraining sheet for about two weeks. The serum injections seemed to modify the clinical condition but little. The heart became very weak, would be cyanosed for several days at a time, and active stimulation had to be resorted to. Twenty-four hours afterward the temperature fell to normal (the twenty-fifth day) clinical improvement was noted—rigidity of neck became less and patient became rational. From this time on he made a steady improvement and was discharged from the hospital March 27, recovered. The spinal fluid March 7 (twenty-four hours after the administration of the first serum) showed diminution in the number of organisms; March 8, still further reduced; and March 9, no organisms found. March 11, several pairs of extracellular diplococci found. Three subsequent punctures were made and 45 c.c. of serum given, principally because of the clinical symptoms; these measures possibly were unnecessary.

Leucocyte Count.—On admission 18,200; twenty-four hours after the first serum injection 21,900; twenty-four hours later, 13,400. The next day (March 9) rose to 20,800 coincident with the development of a parotitis (right); reached 36,200 five days later, when incision and drainage of the gland brought it down to 13,500 five days later.

CASE 10.—*Patient.*—White, male, aged 23, real estate broker. Admitted to the George Washington University Hospital March 16, 1908; patient of Dr. Arthur Hooe.

Onset of Present Illness.—Began March 15, with a well-marked chill, followed by fever and intense headache, which persisted throughout the day and

night. Patient first seen morning of 16th by Dr. Hooe, who found him dull, talking excitedly when aroused. Intense headache and pain in posterior cervical region. Temperature 102, pulse 90, respirations 24. Pupils normal; photophobia. During the day he became delirious and comatose forty-eight hours later. Taken to the George Washington University Hospital 10:30 p. m. March 16.

First Physical Examination.—March 17 by Dr. T. A. Claytor in consultation. Patient semiconscious; knee-jerks normal; Babinski's sign unsatisfactory; Kernig's sign markedly present in both limbs; respiration irregular; pupils contracted and equal; no herpes; neck stiff; head not retracted; superficial reflexes present.

Second Physical Examination.—March 18, 10 a. m., by Dr. Claytor. Kernig's sign still present; coma absolute; pupils equal and contracted; conjunctival reflex present; no herpes or eruption; abdominal reflexes absent; cremasteric reflex absent.

Clinical Course.—March 18. Patient restless and delirious. Knee-jerks decreased. Lumbar puncture at 10:15 a. m. Sixty c.c. of fluid obtained under considerable pressure. This was quite turbid and showed a heavy sediment of thick pus. Gram negative diplococci were found in coverslips, both intracellular and extracellular, the latter more numerous. Thirty c.c. of serum injected at 12:45 p. m. Following the withdrawal of the fluid, patient became very active and was restrained with difficulty. Pulse rose to 180 and dropped to 108 by 8 p. m. At 10 p. m. temperature rose to 102.4, respirations to 32. Examination showed a consolidation of both lungs. March 19: Luxuriant growth of diplococcus in culture from fluid of 18th. Respirations labored; sweating profusely; patient cyanosed; pulse 140 at 10:45 a. m., and weak. Patient took nourishment well. Lumbar puncture at 12:30 p. m. Fifteen c.c. of fluid obtained under very little pressure. Pus much diminished, only a thin granular layer at bottom of flask. Coverslips showed very few organisms; these were chiefly intracellular and stained poorly. Developed some distention of the abdomen during the afternoon. Cultures negative from fluid twenty-four hours later. March 20, distention of abdomen increased and unrelieved by enemata. Clinical condition as regards meningeal symptoms improved. March 21, patient restless and suffering great pain from abdominal distention; rational. At 11 a. m. laparotomy was performed by Dr. William P. Carr and intestine punctured to relieve distention. Patient reacted from operation, but the distention was unrelieved and he died on March 22 at 4 a. m.

While this was a severe case, the improvement in the meningeal symptoms and the spinal fluid was so marked following the serum injections that there seemed every reason to expect the recovery of the patient, despite a complicating pneumonia, had not the intestinal paralysis supervened. Cultures from the peritoneal cavity at the operation were negative for the diplococcus.

Leucocyte Count.—On the third day, 18,400; on the fourth before the serum injection, 15,800; on the fifth, twenty-four hours after the injection, 13,900; on the sixth, after the second injection of 15 c.c., 11,300. In this case the count dropped before the serum injection, hence no conclusions can be drawn as regards any effect of the serum. It did not rise with the pneumonia.

In the ten cases reported, seven patients have recovered, and three died, giving a mortality of 30 per cent. Omitting Case 2, which was hopeless before the serum was administered, we have a mortality of 22.2 per cent. The epidemic in the District of Columbia, 1898-9, 110 cases, gave a mortality of 81.98 per cent. The reports of numerous observers in the past place the mortality of this disease from 66 to 85 per cent.

before the use of the serum. Up to July 25, 1908, Flexner and Jobling[2] report 393 patients treated with the serum, of whom 295 recovered and 98 died—a mortality of 25 per cent.

The severity of the infection and clinical course of our cases has been quite irregular. On the whole it may be stated that the serum-injections have been followed by marked improvement in the meningeal symptoms, fall in the temperature, and shortening of the course of the disease. Only two of the patients had any sequelae: one lost an eye, and another had deafness in both ears. Table 1 shows the ratio of twelve characteristic clinical signs for the ten cases.

TABLE 1.

TEN CASES OF EPIDEMIC CEREBROSPINAL MENINGITIS.

RATIO OF CHARACTERISTIC CLINICAL SIGNS.

Cases	Sudden Onset	Headache	Hyperesthesia	Rigidity of Neck	Retraction of Neck	Kernig's Sign	Babinski's Sign	Absence of Patellar Reflex	Opisthotonos	Tâche Cérébrale	Affection of Eyes	Herpes Labialis	Total No. of Signs
M. S. 1.....	+	+	+	+	+	+	−	+	−	+	+	+	10
F. L. 2.....	+	−	+	+	+	−	−	−	+	+	+	−	7
H. G. 3.....	+	+	−	−	+	+	−	−	−	−	+	+	6
M. H. 4.....	+	+	+	−	+	+	−	+	−	+	+	−	8
J. O. 5.....	?	+	−	+	−	+	−	+	−	−	−	+	5
J. J. 6.....	+	+	+	−	+	+	−	−	+	−	−	−	6
W. B. 7.....	+	+	+	+	−	+	−	−	−	−	−	−	5
E. N. 8.....	+	−	+	+	+	+	−	−	−	+	−	+	7
T. L. 9.....	+	+	−	−	+	+	−	+	−	−	+	+	7
C. W. 10.....	+	+	−	+	−	+	−	−	−	−	−	−	4
Ratio of Cases to Positive Signs.....	9	8	6	6	7	9	0	4	2	4	5	5	

A tabulated summary of the ten cases, with especial reference to the serum treatment and bacteriologic work is given in Table 2.

The earliest day of the disease on which the serum was injected was the fourth; the latest, the forty-ninth. In six cases injections were between the seventh and thirty-fourth day, all patients recovering.

2. Flexnor, Simon, and Jobling, James W.: An Analysis of Four Hundred Cases of Epidemic Meningitis Treated with Antimeningitis Serum, Jour. Am. Med. Assn., July 25, 1908, li, 271.

TABLE 2.

EPIDEMIC CEREBROSPINAL MENINGITIS.

ANALYSIS OF TEN CASES TREATED WITH ANTIMENINGITIS SERUM.

Case	Age	Sex	Day of Disease Anti-Serum Injected	Number of Lumbar Punctures Made	Total Amount of Anti-Serum Injected	Result*	Complications	Sequelæ	Duration (days)	Diplococcus Intracellularis		Other Organisms	Amount of Serum Injected, and Number of Injections Before Organism Disappeared in Coverslip.
										Culture	Coverslips		
1	18	F	6	12	165 c. c.	R	Parotitis. Cystitis. Chorioiditis (R). Arthritis.	Blindness of right eye:	56	+	+	.....	30 c. c. 1 injection. Reappeared. 75 c. c. 7 injections.
2	5 mos.	M	49	5	30 c. c.	D	Chronic hydrocephalus on admission.	Autopsy.....	62	+	+	Bacilus. Influenza group in culture and coverslip.	15 c. c. 1 injection. Both organisms.
3	4	M	7	3	30 c. c.	R	None	None	21	—	+	.....	30 c. c. 2 injections.
4	6	F	4	1	15 c. c.	R	Paralysis of auditory nerve.	Deafness in both ears.	19	+	+	.....	15 c. c. (only 1 puncture made)
5	25	M	8	2	20 c. c.	R	None	Impaired mentality.†	40	+	+	.....	15 c. c. 1 injection.
6	16	M	34	2	15 c. c.	R	None	None	49	+	+	Gram. Neg. B. in coverslip.	15 c. c. 1 injection. Both organisms.
7	39	M	4	6	105 c. c.	D	Pneumonia. Myocarditis and dilatation of right heart.	Autopsy.....	25	+	+	.....	90 c. c. 4 injections.
8	3	M	8	2	15 c. c.	R	None	None	19	—	+	.....	15 c. c. 1 injection.
9	17	M	14	12	142.5 c. c.	R	Suppurative parotitis.	None	35	—	+	.....	97.5 c. c. 5 injections.
10	23	M	4	2	45 c. c.	D	Pneumonia. Intestinal paralysis	No Autopsy...	8	—	+	.....	45 c. c. 2 injections. Faint staining of organism at 21 puncture.

* D—died. R—recovered. † This patient has since recovered perfectly.

Observation of the duration of the cases, from the first serum-injection to discharge from the hospital, is as follows:

Case.	Duration.	Outcome.
1	52 days.	Recovery.
2	13 days.	Death.
3	14 days.	Recovery.
4	15 days.	Recovery.
5	32 days.	Recovery.
6	15 days.	Recovery.
7	21 days.	Death.
8	11 days.	Recovery.
9	21 days.	Recovery.
10	4 days.	Death.

The largest dose administered at any one time was 30 c.c.; the smallest, 5 c.c. In five instances more serum was injected than fluid withdrawn from the spinal canal. All injections have been made into the spinal canal. None of the cases were injected as early in the disease as they probably should have been, and this may have influenced the necessity for the various larger doses which had to be employed.

Observation as to the amount of serum injected before the diplococcus disappeared from the spinal fluid, both in coverslips and cultures, shows:

No. Cases.	Amount.	No. Injections.	Outcome.
5	15 c.c.	1	1 death.
1	30 c.c.	1	
Organism reappeared.			
	75 c.c.	7	Recovery.
1	30 c.c.	2	Recovery.
1	45 c.c.	2	Death.
1	90 c.c.	4	Death.
1	97.5 c.c.	5	Recovery.

The *Diplococcus intracellularis* was found in coverslip preparations in all the cases; in culture in seven of the cases. Two (2 and 6) were cases of mixed infection, one with a bacillus of the influenza group, and the other with a gram negative bacillus which did not grow on artificial media and could not be identified. It is of interest to note that the bacillus disappeared in Case 2 following the serum-injection, and probably also in Case 6.

Observations were made, before and after the serum-injections, on the influence of the serum on the number, appearance and growing properties of the diplococcus to phagocytosis; on the appearance of the leucocytes, and the influence of the serum on the number of leucocytes per c.m. in the circulating blood, and also coincidently the number in the spinal fluid.

INFLUENCE OF THE SERUM ON THE NUMBER, APPEARANCE AND GROWING PROPERTIES OF THE DIPLOCOCCUS.

In two of the cases no lumbar punctures were made subsequent to the injections. There are therefore only 8 cases to be considered.

Number.—In three none were found; in four they were much diminished; in one there was considerable increase five days after one injection of 15 c.c. They disapeared in two days with two injections of 30 c.c. each.

Appearance.—Before injection all cases showed good staining properties. After injection, in three cases (which at the puncture gave negative cultures) it was poor; in one case, fair; in four cases, none were seen.

Growing Properties.—In three cases the diplococcus never grew, leaving only five cases for observation. In two of these it failed to grow following one 15 c.c. injection; in two cases following one 30 c.c. injection. In one of these it reappeared and there were required 75 c.c. in seven injections before the cultures became negative. In one case it required 60 c.c. in three injections before negative cultures were obtained.

RELATION OF THE DIPLOCOCCUS TO PHAGOCYTOSIS.

In five cases there was no change; in two cases, phagocytosis was much increased; in one case it was indeterminable, owing to disintegration of leucocytes. No subsequent punctures were made in two cases.

APPEARANCE OF THE LEUCOCYTES IN THE SPINAL FLUID.

All cases showed good staining before injections. In two cases there were no subsequent punctures. Three cases were not changed by the injections. Five cases showed degenerative changes, from a granular appearance to complete disintegration.

LEUCOCYTE COUNT.

The counts before the injections ranged from 11,800 to 30,800. In two of the cases, unfortunately, no counts were made. Following the injections the counts rose in three cases: One remained high and was probably kept up by complications; one had no complications; one rose, later fell considerably, then rose with a complicating parotitis and fell on incision of gland.

The count fell in five cases; in two, it fell progressively; in one it rose again and then progressively fell; in one, rose again with a complicating pneumonia, and then progressively fell; in one, it fell before injections.

RELATION OF THE LEUCOCYTE COUNT TO THE NUMBER OF LEUCOCYTES IN THE SPINAL FLUID.

This observation could be made in only seven of the cases, and the data available in these were too meager to be of any value. In five of the seven there was a rise in the count coincident with a decrease of cells in the spinal fluid, or vice versa. In the other two there was a fall with a decrease.

SUMMARY.

1. In ten cases of epidemic cerebrospinal meningitis treated with the antimeningitis serum, seven patients recovered, and three died, giving a mortality of 30 per cent. Omitting one of the cases, which was one of chronic hydrocephalus, we have a mortality of 22.2 per cent.

2. Following the serum-injections there was usually considerable improvement in the clinical symptoms.

3. The course of the disease was considerably modified; an average of twenty-three days for all seven, and in five of the cases, fifteen days.

4. Only two patients who recovered suffered from sequelæ.

5. The serum caused a marked diminution in the number of diplococci in the spinal fluid; a disappearance or degeneration of the organism in coverslips, and in the majority of cases its growth was promptly inhibited.

6. Phagocytosis was either unchanged or increased.

7. In five out of eight cases the leucocytes showed degenerative changes following the serum injections. This explains the rapid clearing of the fluid observed following the injections.

8. The leucocyte count rose in three cases, in all of which the patients recovered. It fell in five cases, in two of which the patients died.

9. The disappearance of the bacillus in Case 2, and probable disappearance of that in Case 6, suggests the use of an indifferent serum in influenza meningitis.

We wish to thank Doctors Boswell, Hooe, Owens, Cook, R. W. Baker, Paul Johnson, Claytor, Acker and Groover, for their courtesies in consultation and association in the various cases.

Garfield Memorial Hospital.

THE BACTERIOLOGY OF ACUTE RHEUMATISM.*

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Since the beginning of modern bacteriology, many observers have believed that acute articular rheumatism belonged to the infectious diseases. Its course, frequently beginning with sore throat and terminating in a relatively short time, its appearance in epidemics and the occasional infection of an attendant, the similarity of the pathologic changes to those occurring in diseases known to be contagious and infectious, stimulated bacteriologists to search for the infectious agent. All types of bacteria were isolated from rheumatic cases, bacilli and cocci, aërobic and anaërobic; each worker had his own specific organism. The diversity of findings led to the conclusion that various organisms might produce identical symptoms and pathologic changes, just as pneumonia might be produced by a variety of bacteria. The occurrence of articular changes, similar to those of rheumatism, in pneumonia, scarlet fever and other infectious diseases made this assumption the more plausible. The view that acute articular rheumatism may be caused by an infection by various organisms—staphylococci, streptococci, pneumococci and others—or by a mixed infection, is still held by a large number of clinicians and bacteriologists.

Of those who believe that rheumatism is produced by a single specific parasite, there are three classes: 1, Achalme and his followers, notably Thiroloix; 2, Triboulet and Apert, Westphal, Wassermann and Malkoff, and their large school in Germany and England—of the latter especially Poynton and Payne; and 3, those who do not believe that the organism has been found.

ACHALME'S ANAEROBIC BACILLUS.

Achalme, in 1891, at the autopsy of a man who had died on the fourth day of an acute articular rheumatism with cerebral manifestations, discovered and grew in pure culture an anaërobic bacillus. It is a large organism, which in human tissues, or when on media prepared from human blood or urine, resembles the bacillus of anthrax; at times it is almost filamentous. It is not motile or very feebly so, stains by Gram's

*From the Dane-Billings' fellowship in medicine, Rush Medical College, in affiliation with the University of Chicago.

method and with difficulty may be made to produce spores. In 1897 Achalme reported a second autopsy with similar findings: in the interval he had found the same organism in six living patients, four times in pure culture. Thiroloix had also found the anaërobic bacillus in nine cases of rheumatism, and other French and Italian observers a few times. In both of Achalme's autopsies, the bacillus was present in enormous numbers in the heart's blood and pericardial fluid; in smaller numbers, but also abundantly, in the cerebrospinal fluid, in the myocardium and diseased heart valves.

Inoculation of 1 c.c. of a bouillon culture in guinea-pigs produced death by septicemia in ten hours without local lesions. It resulted in vasodilatation, widespread thromboses, necroses, and the appearance of many mast cells at the site of inoculation. Thiroloix produced lesions in rabbits resembling those of rheumatism: endocarditis, pericarditis and pleurisy.

There is little ground for belief in the specificity of Achalme's bacillus, or at any rate for an assumption that it plays a rôle in many cases of rheumatism. During the last ten years an enormous amount of time has been given to the study of the bacteriology of the disease, and not more than eight or ten observers have found the organism; even those in a very limited number of cases. In the second place, the results of inoculation are most unsatisfactory. The general manifestations in animals have not resembled those of rheumatism in the human being. As a rule, the animals have died within a few hours. Endocarditis, pericarditis and pleurisy have been produced in animals by the inoculation of practically all of the known pathogenic bacteria — streptococcus, staphylococcus, pneumococcus, tubercle bacillus, etc., and their occurrence here does not make the specificity of the bacillus more probable. Recently Achalme has stated that his bacillus is identical with the *Bacillus aërogenes capsulatus* of Welch and Nuttall. He still believes it responsible for some, but not all cases of rheumatism.

THE STREPTOCOCCUS OF TRIBOULET AND APERT.

Triboulet and Apert, in 1898, produced mitral disease in a rabbit by the injection of streptococci obtained from a patient with rheumatism.

In 1899, Westphal, Wassermann and Malkoff isolated a streptococcus from a fatal case of chorea, following rheumatism, which they believed to be specific. The organism was found in pure culture in the heart's blood and the diseased valves. Streptococci had been previously found and described as occurring in ulcerative endocarditis consequent upon rheumatism. Von Leyden, in 1894, and Michaelis and Klemperer, in

the following year, had noted similar discoveries, but believed the organism to be one of a number which could give rise to such pathologic changes. Klebs, in 1875, Krause, in 1884, and Mantle, in 1887, had described the finding of streptococci in the joint fluids in rheumatism. Westphal, Wassermann and Malkoff found in addition that their organism, when grown in pure culture, could produce in rabbits changes closely resembling those of rheumatism. In three to ten days following the injection of the organism into the peritoneum, the joints became swollen and tender, the temperature rose several degrees, there was no suppuration, and the disease usually terminated in recovery. They described the organism as a streptodiplococcus, appearing in pairs and in short chains, and as requiring for its growth a high degree of alkalinity and a large amount of peptone in the culture media. This discovery gave a new impetus to the bacteriologic study of the disease. Since 1899 a host of investigators have given their attention to rheumatism. Poynton and Payne, of London, began their study, believing that they might reach the conclusions of Achalme and Thiroloix; in a short time they were followers of the other school. Poynton and Paine, Beattie, Shaw, Beaton and Walker, and many others in England have become convinced of the specificity of the organism. Unfortunately, most of their cultures have been derived from the cadaver. Since the researches of Flexner on terminal infections, it is well known that various organisms proliferate freely in the human body and appear in the circulating blood before death, so that it is possible that the organism found in the heart's blood may have been the ordinary *Streptococcus pyogenes*. The English observers have produced in rabbits practically all the symptoms and complications of rheumatism, as found in the human being; joint involvements, endocarditis, pericarditis, pleurisy and peritonitis. In at least three instances they (Poynton and Paine, Beaton and Walker, and Beattie) assert that they have observed choreiform movements in the head and eyes of the rabbits. Positive results have also been obtained from cultures of the circulating blood and joint fluid. The study of the morphology and cultural characteristics of the streptococcus has given varying results. In general it has been found that the organism does not differ in appearance from the *Streptococcus pyogenes*, except that the chains are usually short, containing not more than ten organisms, and that the chains are divided into pairs. Poynton and Paine maintain that acid media are most favorable to its development, while Beaton and Walker agree with Westphal, Wassermann and Malkoff in preferring alkaline agar and bouillon. The growths correspond rather closely to those of the *S. pyogenes* and to that of the organism of scarlet fever, as

described by Aronsohn and Moser. They are hemolytic, turning blood media to a rusty brown or chocolate color. Cultures on liquid media are not agglutinated by the serum of a rheumatic human being or that of convalescent rabbits.

EXPERIMENTS OF MEYER AND OTHERS.

Contradictory results have been obtained in large numbers. Phillip failed to grow the organism in twenty-one cases in which blood cultures were attempted, and in six inoculations from the knee joint. Meyer was likewise unsuccessful in thirty cases.

The work of Meyer is the most original and interesting of any done on the subject in recent years. He concluded, from his unsuccessful search of the blood, that the disease was either an intoxication from bacteria which remained localized in the throat or that the organisms entered the blood and were there rapidly destroyed. His method of studying the throat bacteria is unique. It is a thankless task to try to isolate the various organisms by agar plates or similar methods. He therefore inoculated bouillon with swabs from the throat, and after twenty-four hours' growth in the incubator, introduced some of this bouillon into the ear vein of rabbits. His results were remarkable. In a few days only one species was found in the joints; their localization he regarded as a sign of special affinity. These organisms, when grown in pure culture and again introduced into rabbits, produced just such results as had been described by Triboulet, Westphal, Wassermann, Poynton and others. They also presented a close resemblance morphologically. The blood and joint fluids were sterile within a few days, but cocci were found in large numbers in the endothelial lining of the joints and of the heart valves affected.

The conclusions as to specificity of the streptococcus reached by Meyer would be very convincing if there were not contradictory evidence. Bezançon and Griffon, in 1899, however, while trying to immunize rabbits against pneumococci, found that attenuated cultures frequently produced joint changes, pericarditis and pleurisy, such as had been described in connection with the streptococcus. Meyer, too, is compelled to assume that in scarlet fever, typhoid fever and other diseases, the transient arthritides are produced by a mixed infection.

Efforts to distinguish morphologically and culturally between this and other streptococci have been unavailing. Beaton and Walker found that it produced formic acid and that it grew on filtered bouillon, in which the *S. pyogenes* has been previously cultivated; to the latter fact (Marmorek's test) has been given special prominence.

Walker, in one of his latest paper on the subject, admits that "the case in favor of the *Micrococcus rheumaticus* is non-proven and appears, in some respects, perhaps less favorable than it did four or five years ago." The morphologic methods of differentiation have suffered especially. He enumerates the differential characteristics as follows:

1. A greenish brown discoloration in blood agar cultures, due to reduction of the hemoglobin. (This was shown by Schottmueller in 1903 to be true of various streptococci).

2. Growth obtained in Marmorek's test, that is, a filtered bouillon, on which other strains of streptococci had been grown. (The value of this test was made doubtful by the work of Meyer and Aronsohn in 1902.)

3. Growth in very alkaline media.

4. Production of considerable quantities of acid. (Neither of these characteristics is sufficiently distinctive to differentiate.)

Walker also says that he has "no hesitancy in saying that, as far as its appearance and characteristics went, the organism would undoubtedly be classed as an ordinary streptococcus, if handed without comment to an expert bacteriologist."

Admitting the impossibility of distinguishing the organism described, morphologically and culturally, two more methods remain for its identification as the specific cause of rheumatism: 1, its discovery in all cases of the disease; and 2, the production of the disease in animals by its introduction into their bodies. As mentioned before, the second point has been most emphasized. The work of Beattie and Meyer has been especially important. Beattie compares the results of inoculation in rabbits of the *Streptococcus pyogenes* with those produced by the *Micrococcus rheumaticus*.

STREPTOCOCCUS.

Method of Injection.	No. Subjects.
Intravenous	34
Intraperitoneal	7
Subcutaneous	3
Subcutaneous and intraperitoneal	4
	48

Results.	No. Subjects.	Per cent.
Death in	7	14.5
Arthritis in	9	18.7
Endocarditis in	1	2.

"MICROCOCCUS RHEUMATICUS."

Method of Injection.	No. Subjects.
Intravenous	13
Knee joint	1
Subcutaneous	1
	15

Results.	No. Subjects.	Per cent.
Death in	2	13.3
Arthritis in	9	60.
Endocarditis in	5	33.3

In the former the arthritis was definitely purulent and usually involved the wrist joints. The only case of endocarditis was associated with abscesses of the kidney and vertebræ. The arthritis of the latter was nonpurulent and usually appeared in the knee joint. Most of the animals that were not killed recovered from the disease.

Meyer's results were similar, although the percentages differed. Of one hundred animals inoculated with the specific organism, twenty-one developed joint disease, while only two of one hundred treated with *Streptococcus pyogenes* exhibited arthritides. Transplantation and animal passage did not increase its tendency to suppuration. Lewis and Longcope inoculated five rabbits with a streptococcus derived from a fatal case of rheumatism twelve hours antemortem; all of the animals showed joint involvement, and one a vegetative endocarditis.

The power of the streptodiplococcus to produce joint disease and its special affinity for the joints is beyond question, but the experiments of Widal, Benzançon and Griffin, and of Cole, have rendered it doubtful whether other organisms may not also act as causative factors in the disease.

Demonstration of the coccus in all cases of the disease has failed most signally. Cole states that for years blood cultures were taken from every case of rheumatism at the Johns Hopkins Hospital, and that these had been invariably sterile; the results of Singer and Phillip were similar. While some of the positive findings of the English observers were obtained in living individuals, the vast majority were derived from the cadaver; the endocardium and synovial membranes appear to be particularly rich in organisms. The blood and synovial fluids were usually sterile at autopsy. The type of rheumatism in England must be much more severe than that seen in this country or on the European continent, as fatal cases of uncomplicated rheumatism are unusual with us; hence the opportunity of studying them bacteriologically at autopsy rarely presents itself. The postmortem study is also associated with dangers. The multiplication of bacteria in the body shortly before death is well known, and their discovery in large numbers may lead to false conclusions. Could similar results be obtained in the living and not moribund, they would be of much greater value in the establishment of the organism as the specific agent. It was with this object that my work was undertaken.

REPORTS.

This work consisted of attempts at cultivating the suspected organism from forty-five cases, all of which were clinically typical of acute articular rheumatism. The cases were taken as the patients entered the Cook County and Presbyterian Hospitals; those which had passed the acute febrile stage were rejected. The large majority had received no medical treatment, or at most a few doses of the salicylates at the time the culture media were inoculated. Relatively few of the patients came under observation during the first week of the illness; almost all during the second week. By this time there were evidences of throat infection only in isolated instances, though the majority gave a history of early involvement of the tonsils.

The media used were at the beginning those recommended for the purpose by Poynton and Paine and their school in England. It was found almost impossible, however, to produce clear alkaline broths and agar; this made the determination of the presence of growths by the naked eye very difficult. All of the liquid media presented precipitates after intervals of twenty-four to seventy-two hours; these probably consisted of minute flakes of fibrin, which adhered to the side and bottoms of the tubes and flasks. When growths were obtained, they were inoculated into all of the special media prepared, as well as on ordinary agar, blood serum, acid bouillon, and litmus milk. It appeared that the growths in acid bouillon were more luxuriant and rapid than those in the original cultures; therefore, in the latter part of the work, acid bouillon was employed for the first inoculations and if growths were present subcultures were made from them. As it was difficult at times to be sure whether or not there would be a positive result, inoculations were made from all of the primary flasks in twenty-four to forty-eight hours after their inoculation. In every case in which any growth was obtained, from 15 to 30 c.c. of a culture in bouillon was introduced into the ear veins of one or two rabbits. In each case the inoculation was repeated if the rabbit lived.

Many of the patients had mild endocarditis; four had ulcerative endocarditis; of these two recovered. One of these in the course of his illness had a hemiplegia. Of the two fatal cases, the diagnosis in one was confirmed by autopsy. The patient in the other case had a pericarditis in addition to the endocarditis. Another patient had enormous subcutaneous and submucous hemorrhages. Almost the entire body surface was discolored purple or dark red. The slightest traumatism produced hemorrhages, and the introduction of the needle into the median

veins also resulted in enormous effusions. The rheumatic symptoms in this case had also been very pronounced, but had become much less marked when the bacteriologic work was undertaken. The patient died within a week of the time at which blood was taken from his veins, but no autopsy could be made.

Blood was taken from the most prominent vein at the bend of the elbow in each one of the cases. For this purpose a Luer syringe, which had been sterilized in the autoclave, was used and a needle sterilized by dry heat. No joints of any kind were used and no lubricant to make the syringe air-tight. These things were discarded so as to minimize the chances of contamination. It was usually possible to obtain 7 to 10 c.c. of blood in this way. In the earlier part of the work 1 c.c., 3 c.c., and 5 c.c. of blood, respectively, were introduced into three flasks containing 150 c.c. of bouillon; in the latter part two flasks only were used, for one of which 2 to 3 c.c. of blood were used, and 5 c.c. for the other. When possible, fluid was also taken from the joints. In many cases, in spite of the apparently large effusion into the joints, it was impossible to obtain any fluid. The difficulty seemed to be less in the viscidity of the fluid than in the fact that the greater part of the swelling was due to edema of the surrounding tissues. The skin at the point of introduction of the needles was sterilized, as well as possible, by the use of 95 per cent. carbolic acid, followed by alcohol.

Of the forty-five cases thus examined, thirty-four gave no cultures at any stage. In five of these, fluid from the knee also gave no growths. Of the remaining eleven cases, cultures were obtained in ten cases from the blood, in one case from the knee joint.

CASE 1.—Two blood inoculations were made; of these one was negative, 1 c.c. of blood in 100 c.c. of bouillon. One of 3 c.c. of blood in 100 c.c. of bouillon showed an abundant growth in twenty-four hours. The bouillon was very turbid. Microscopically, smears showed numerous cocci not arranged in chains or pairs. Subcultures corresponded to growths of the *Staphylococcus albus*. No further work was done with this culture, as it was assumed to be either a contamination or derived from the skin.

CASE 2.—A luxuriant growth appeared in all the culture flasks in twenty-four hours. Subcultures in glycerin agar appeared as white, pinhead-sized colonies. Milk was not acidified in twenty-four hours. Smears showed staphylococci, which were large, many biscuit-shaped, and sometimes arranged in pairs, never in chains. Inoculation into a rabbit produced no apparent change. This, too, was assumed to be a contamination and the organisms were traced no further.

CASE 3.—This was a case of joint involvement associated with high temperature and cerebral manifestations, resembling those of a meningitis. My cultures during life were negative. At autopsy, minute warty vegetations were found on the mitral valves. The joints were not opened. Cultures taken from the blood and meningeal fluids showed a motile bacillus, which did not produce rheumatic

changes in a rabbit. The organism was a facultative anaërobe, resembling in appearance the typhoid bacillus. It was not identified.

In none of the above cases could any suspicion be entertained that the organism isolated was that believed to be specific for acute articular rheumatism. In all the following a streptodiplococcus was obtained, which morphologically and culturally corresponded to that described by Triboulet and Apert, Wassermann, and Poynton and Paine. All the cases were recent and undoubted acute rheumatics.

CASE 1.—Growth appeared in twenty-four hours. Inoculations into ear veins of two rabbits were negative.

CASE 2.—Cultures did not become apparent until after six days in the incubator. Inoculations were negative.

CASE 3.—Rheumatism with malignant endocarditis and pericarditis. Inoculation into rabbit (10 c.c. of bouillon culture) produced death in twenty-four hours. Heart valves and joints showed no changes.

CASE 4.—There was slight turbidity in twenty-four hours. Inoculations were negative.

CASE 5.—Rheumatism with acute endocarditis and hemiplegia. Growths on all media showed typical organisms. Inoculation into one rabbit produced death in a few hours; autopsy showed a thrombus in the right ventricle. Inoculation into other rabbits caused no perceptible change.

CASE 6.—The original culture showed no visible growth. A subculture on glycerin agar in one week presented very minute colonies above the water of condensation. Short chains (six to eight cocci) were found in the smears. Inoculations into animals proved negative.

CASE 7.—Malignant endocarditis associated with rheumatism. Inoculations into rabbits produced no apparent effect.

Only one positive culture was obtained by the use of joint fluid.

CASE 1.—This culture was taken from the right knee. Growths appeared in twenty-four hours. These resembled in all particulars those obtained from the blood in the preceding seven cases. Inoculations into rabbits were negative.

In five cases, joint cultures remained sterile.

Blood cultures were also made from two cases of chorea. Both of these showed growths on all media.

CASE 1.—Previous rheumatism; second attack of chorea. Cultures were positive in two days. Smears showed Gram-positive diplococci and staphylococci. The growths appeared as white colonies, pinhead-sized, to a great deal larger. Subcultures were typical of *Staphylococcus pyogenes albus*. Inoculations into a rabbit produced no noticeable symptoms.

CASE 2.—Mother of patient had had rheumatism twenty-two years before; one sister had had chorea four times. Blood smears were made on glycerin agar; subcultures in bouillon, which became markedly cloudy after days. Smears showed diplococci longer than broad, with the general characteristics (noted before) of the *Streptococcus pyogenes*. Inoculations into rabbits were negative.

Altogether, then, a streptodiplococcus or streptococcus was isolated from nine cases:

Five were of rheumatism with or without endocarditis of a mild type (four from blood, one from knee).

Three were of rheumatism with malignant endocarditis.

One was a case of Sydenham's chorea.

Other organisms were obtained in four cases, one undoubtedly a contamination; three proved to be the *Staphylococcus albus*. It is more than likely that this organism came from the skin of the patient, in which it is found so frequently that it must be reckoned with as a finding in a fairly large percentage of blood cultures.

On the basis of such findings Sahli and others have contended that rheumatism might be produced by any one of a number of organisms. Nevertheless, the staphylococcus at least is of such frequent occurrence in association with other diseases or cultures from normal blood that its discovery must in most cases be attributed to other sources than the circulating blood.

It is difficult to draw any positive conclusions from my work. I believe it unlikely that the streptococci obtained from the blood in the above cases were identical with those cultivated by Wassermann, Poynton, Paine and others, chiefly because they failed to show the only feature which distinguishes them from other streptococci, their virulence and the production by them of specific pathologic changes in animals. As stated above, cultures and morphologic appearances of the "*Micrococcus rheumaticus*" differ in no essentials from those of other types of streptococci. All the characters supposed to belong particularly to the coccus of rheumatism have been shown to occur with other strains as well. The failure to isolate a virulent streptococcus from the blood does not, however, disprove its existence; there may be truth in the contention of Meyer that the blood is an unfavorable medium, and that the organisms fail to proliferate, and die except when located in the fixed tissues. Animal inoculations with the streptococcus seem to confirm this hypothesis. In many other diseases, too, in which there may be a generalized infection, such as gonorrhea and tuberculosis, the organisms are demonstrated in the blood with great difficulty.

Streptococci have been found in many diseases in which their pathogenicity is far from proved: scarlet fever, smallpox, terminal and other infections. They seem to develop very readily in patients whose general resistance has been lowered. Pathogenic organisms of other types have also been grown from the blood of individuals not suffering from the diseases which these organisms ordinarily produce. Thus Busse has reported the cultivation of typhoid bacilli from the blood of three cases of miliary tuberculosis and one of pneumonia. Krehl (quoted by Busse) reports a similar experience, and the multiplication of blood cultures in clinical work will undoubtedly increase the number. From such evidence

one can judge of the possible source of the organisms obtained by my blood cultures. My results are in accord with those of Singer, Philip, Cole and Meyer, who also failed in their attempts to grow the *Micrococcus rheumaticus* from the blood of patients. It would be folly to deny on such grounds the existence of a specific organism; but it appears that isolation of the coccus from the living body is necessary to fix its position as the specific cause of rheumatism. Postmortem examinations are fraught with too many fallacies, and the organism shares with too many others the faculty of producing rheumatoid lesions, though it may do so with greater frequency. Until the coccus is proved to occur in most of the living patients as well as in the fatal cases of rheumatism, the claims for its specificity will remain on an unstable foundation.

[I wish to thank the attending physicians of the Cook County and Presbyterian hospitals for their kindness in permitting the use of their patients, and especially Dr. Billings for the opportunity of doing this work.]

100 State Street.

A CLINICAL AND PATHOLOGIC STUDY OF A CASE OF ADAMS-STOKES' DISEASE.*

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AND

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This disease, which was first described by Adams[1] in 1827, did not receive general recognition until 1846; at this time Stokes[2] published his studies of the subject and presented a more complete clinical picture. After this it was known as Adams-Stokes' syndrome. In the past few years, since the pathology has been more definitely determined, it is usually described as Adams-Stokes' disease.

The disease is perhaps not as rare as one is led to believe in looking over the literature. Michael and Beutlemiller[3] were able to collect about seventy cases, the majority of which were reported in the last few years. The fact that cases are more frequently reported in recent years is due to the great interest aroused by the discovery by His of the auriculoventricular bundle and to the studies of the physiologic function of this bundle by Erlanger.

While we do not feel it necessary to report our case to help prove the correctness of the relation existing between disease of the bundle and the symptoms of Adams-Stokes' disease, we do feel justified in presenting it because it is a unique case in so far as the character of the pathologic lesion is concerned, and, therefore, adds at least something of interest to the subject.

Before Gaskell, His, Jr., Tigerstedt and Erlanger demonstrated, by ingenious experiments, that the symptoms of Adams-Stokes' disease and those of heart-block were practically identical, numerous theories were advanced as to the cause of this condition. Stokes himself approached more closely to the true nature of the underlying pathologic basis when

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* This article is illustrated from negatives which were made in color by the Lumière process direct from the specimens.

1. Adams: Dublin Hosp. Rep., 1827, iv, 396.
2. Stokes: Dublin Quart. Jour. Med. Sc., 1846, ii, 73.
3. Michael and Beutlemiller: Berl. klin. Wchnschr., Nov. 18, 1907, xliv, 1474.

he suggested that the lesion was in the heart muscle. Charcot suggested that the lesion was in the medulla. Houchard[4] held that there was present a disease of the cerebral vessels associated with a disturbance of the mechanism of the heart.

Gibson[5] and Jacquet[6] recognized the presence of heart-block, and thought that there was a similarity with intermittent claudication. By others it was recognized as fatty degeneration of the heart muscle and tumors of the vagus, or pressure on the vagus. In spite of the fact that the results of the recent investigations by His, Jr., and his coworkers seem so conclusive, there still appears to be some disparity in opinion as to the cause of this disease. Thus Pearson[7] holds that the existing cause resides at different levels of the nervous mechanism.

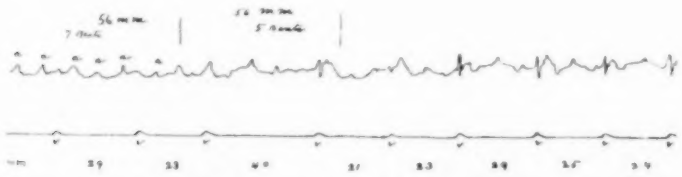

Fig. 1.—Pulse tracing of patient described in case history; *a*, auricular pulse; *v*, ventricular pulse. Lower figures represent the difference between each ventricular pulse in mm.

The many interesting studies on the physiology of the heart, especially those relating to the cause of its rhythmic action, all tend to confirm the view of those who favor the theory of the myogenic origin of the condition and tend to disprove the neurogenic theory. It has been demonstrated that the inherent rhythmicity is not dependent on the nervous mechanism, although it has a governing influence over it. In favor of this view may be mentioned the fact that, in the fetal heart, contractions occur before the nervous system is developed.

In the myogenic theory, it is assumed that the impulse passes from the auricle to the ventricle and that there is a brief interval between the contraction of the auricle and the contraction of the ventricle. In the mammalian heart, it has been found that by warming or cooling the area between the mouths of the two venæ cavæ, the heart-rate can be modi-

4. Houchard: Traité des maladies du cœur.
5. Gibson: The Nervous Affections of the Heart, 1904, p. 65.
6. Jacquet: Deutsch. Arch. f. klin. Med., lxxii, No. 2.
7. Pearson: Dublin Jour. Med. Sc., October, 1907.

Fig. 2.—The color photograph of the heart shows the heart laid open, exposing the endocardium of the left ventricular septum. The calcareous nodule at the base of the segment of the mitral valve is well shown and in the cross section of the muscle of the left ventricle a calcareous nodule is seen just below the base of one of the cusps of the aortic valve. (Prof. W. T. Simon.)

fied,[8] and as this is the only area which influences the whole heart's action[9] it is safe to assume that the impulse begins at this point and passes through the auricle into the ventricle. The assumption that this impulse is conducted through the muscular fibers led to the natural inference that there must be a connective bundle between the auricle and the ventricle.

In 1893 His, Jr.,[10] described a muscular bundle connecting the auricle and ventricle through the auriculoventricular septum. Little attention was paid to the discovery of His until 1904, when Retzer,[11] Brauning,[12] and Humblet[13] confirmed His' observations and gave a complete description of the anatomy of the bundle of His.

A number of observers have contributed articles on the dissociation of the auricles and ventricles. Stannius,[14] in 1852, first observed this phenomenon in cold-blooded hearts after ligation of the sinoauricular junction. The results obtained experimentally by this method are fully described by Gaskell,[15] who succeeded in producing independent auricular and ventricular contractions in the heart of a tortoise by constricting the circular layer of the muscles at the auriculoventricular junction. Wooldridge,[16] in the same year, was able to sever the functional connection between auricles and ventricles by crushing the tissue in the auriculoventricular junction. This had the effect of producing an independent rhythm for both auricle and ventricle and a marked slowing of the ventricles. His, Jr.,[17] in 1905, demonstrated the same condition by simply destroying the auriculoventricular bundles.

In 1905 Hering confirmed His' experiments. At the same time Erlanger was performing his valuable experiments, but using different methods. Erlanger's results are best described in his own words:

> With gradual compression of this bundle, the following phenomena may be noted: First may be seen a slight increase in the interval between the beginning of an auricular and the beginning of its independent ventricular contraction. This, then, is the first sign of heart-block. With further clamping, a degree of

8. McWilliam: The Rhythm of the Mammalian Heart, Jour. Physiol., 1888, ix, 167.

9. Adam: Pfluger's Arch., 1906, cxi, 607.

10. His, Jr.: Arb. an d. med. klin. zu Leipzig, 1893, p. 14; Centralbl. f. Physiol., 1895, ix, 469.

11. Retzer: Ueber die musculose Verbinding zwichen Vorhof und Ventrikel des Saugethierherzens, Arch. f. u. Entwcklngsgesch., anat. part, 1904, p. 1.

12. Brauning: Arch. f. Physiol., 1904, supplement, 1.

13. Humblet: Arch. internat. de physiol., 1904, vii, 278.

14. Stannius: Arch. f. Anat., Physiol. u. wissensch. Med., 1852, p. 87.

15. Gaskell: Jour. Physiol., 1883, iv, 43.

16. Wooldridge: Arch. f. Physiol., 1883, p. 552.

17. His, Jr.: Centralbl. f. Physiol., 1895, ix, 469.

compression may be reached in which this interval, the intersystolic period, gradually increases in length with successive beats until eventually the ventricles fail to respond to one of the auricular impulses. Following this ventricular silence, the intersystolic period is short, but it immediately begins to lengthen again until another ventricular beat is dropped. In this way states may be produced in which ventricular beats may be dropped quite regularly in 10, 9 or 8, etc., auricular beats. With further clamping, more advanced stages of partial block may be obtained, stages in which only every other or every third or every fourth auricular beat may stimulate the ventricles, giving rise to what are generally termed 2:1, 3:1, 4:1, etc., rhythms, respectively. The ventricles may beat independently of the auricles, although the block is not actually complete. This state has been termed relative complete block. Finally, when the pressure on the auriculoventricular bundle becomes such that the auricular impulse fails to pass the obstruction, the block becomes absolutely complete. In both forms of complete block, the ventricles beat more slowly than the auricles, and independently of them. This state of affairs is seen in advanced stages of Adams-Stokes' disease.

In relative or partial heart-block, the rhythm of the ventricles is influenced by the rate of the auricular contractions. Experiments seem to demonstrate what is borne out by clinical observations (Fig. 1) that the auricular impulse is inverse to the auricular rate. Therefore, when the auricles beat rapidly, the impulses are not of sufficient strength to stimulate the ventricles to contraction, and the rhythm which becomes more complete may change from 2:1 to 3:1 to 4:1, etc., or even complete block may ensue. In this connection it is interesting to mention the effect of stimulation of the vagus and accelerator nerves in both partial and complete block.

Both the vagi and accelerators have very slight influence on the rate of the ventricles during complete block, but the auricles are affected as usual.

Usually, at the moment when partial block passes into complete block, the ventricles cease to beat altogether, until they are stimulated to an independent action by their inherent rhythmicity. It is at this stage of Adams-Stokes' disease that the syncopal attacks develop, and these attacks are invariably associated with the so-called stoppage of the ventricles. Erlanger and Hirschfelder[18] made a series of experiments with the object of studying the phenomenon of stoppage of the ventricles and its relation to the syncopal attacks of Adams-Stokes' disease. The results of these experiments were overwhelmingly in favor of the view that "the ventricles cease to beat for a time, when they are no longer whipped into action by their physiologic stimulus, because some time is required for

18. Erlanger and Hirschfelder: Further Studies on the Physiology of Heart-Blocks in Mammals, Am. Jour. Physiol., 1906, xv, 153. Hering, H. G.: Arch. f. d. ges. Physiol., 1905, cvii, 97.

Fig. 3.—This shows a photograph of the gross specimen and at C the large irregular calcareous nodule is seen. B indicates the calcareous area just in the region of the bundle of His, as it comes from the auricle, and A shows the irregular calcareous column beneath the endocardium which pressed upon the bundle of His in its course between the fibrous ring and the ventricular septum. D shows the branching of the bundle just beneath the endocardium of the left ventricle. (Dr. T. M. Wright.)

the dormant inherent rhythmicity of the ventricles to acquire its maximum efficiency." Erlanger and Hirschfelder were inclined to believe that the syncopal attacks result from the sudden cessation of the influence of the auricles over the ventricles. They observed that in one of their cases the ventricular stoppage was always preceded by an acceleration of the auricles. This also occurred in our case.

CLINICAL OBSERVATIONS.

Patient.—A man, aged 72, with a splendid family history. With the exception of malaria from the age of 14 to 40 years, while residing in Virginia, and two attacks of pneumonia between 50 and 60 years of age, the patient had enjoyed remarkably good health. His occupation was blacksmithing and steel inspecting, which he followed actively until the summer of 1907. He was an inveterate smoker for years, and occasionally took a glass of beer; otherwise his habits were most exemplary.

Onset of Symptoms.—This dates from an injury which he sustained July 9, 1907. In crossing the railroad, he stepped underneath the gate which was being lowered, and received a slight blow on the head. He fell and was unconscious for one or two minutes, after which he was able to walk unaided. Four days later a sensory aphasia suddenly developed. This was associated with a slight weakness of the right arm. There were no other evidences of paralysis. The patient remained in bed for several weeks, although he was able to walk. His pulse at this time ranged from 60 to 64, but there was no disturbance of rhythm noted. The aphasia began to subside after one week, and it gradually improved until only a slight hesitancy in speech remained. In a month he was going about freely and doing light work. In the latter part of November he began to have "weak spells," in which he fell, but did not become unconscious. These attacks lasted only a few moments. He was in the habit of walking close to buildings or fences, in order to support himself when an attack came on and prevent himself from falling. The family had noticed that during his sleep he had been breathing irregularly (Cheyne-Stokes) for some time. On Jan. 4, 1908, he was taken with a series of attacks (probably ten within an hour and a half) which we had the opportunity to study. These attacks recurred frequently, although at very irregular periods for the next two weeks, after which occasional attacks developed until they finally disappeared entirely.

Physical Examination.—The patient was a tall, slender, fairly well-nourished individual and appeared much younger than his actual age. The color of the skin and mucous membrane was normal. There was no inequality in the size of the pupils and both reacted promptly to light and accommodation. Arcus senilis was present, but not marked. An epithelioma, the base of which was about the size of a dime, was situated on the right cheek over the malar bone. The tongue was clean and not tremulous. The chest was fairly well developed, and expansion was equal on the two sides. Pulmonary resonance was good and breath sounds were normal. In the recumbent posture, the cardiac impulse at the apex appeared in the fifth intercostal space, directly inside the nipple line. It was slightly diffused, but not heaving in character. No thrill was present. Marked irregular pulsations were constantly seen in the veins, at the base of the neck, averaging from 76 to 90 per minute. The radial pulse was slow, ranging from 26 to 32 per minute, and the tension was minus. The rhythm was not much disturbed, except on those days when the patient suffered with frequent syncopal attacks. The condition of the arterial walls was about normal for a man of the patient's age. The area of cardiac dulness was somewhat increased

in the transverse diameter, more to the right than to the left. No definite murmurs were heard. At the apex, the first sound was feeble, the second was clear and more distinct. Between each ventricular systole were heard faint, short and somewhat indistinct sounds. Their maximum point of intensity was toward the base of the heart, diminishing toward the apex, and lost entirely at the mitral area. There was no evidence of gastrointestinal disease. Liver dulness was normal; the spleen was not palpable and the urine was negative.

Character of Attacks.—The character of the attacks did not vary much, except in degree. Some were apparently much more severe than others. They were usually preceded by a distinct aura, which was in the form of sounds resembling the ringing of bells or music. This was associated with intense pain in the right side of the head and face. There was also spasmodic contractions of the muscles in this area. During this stage the patient raised up in bed, grasped the right side of the face with the right hand and groaned. He soon afterward sank into unconsciousness, which lasted from five to fifteen seconds. During this period the color of the face was an ashen gray; the lips were cyanotic and the breath was slow, irregular and stertorous. After returning to consciousness, he sank his head into the pillow and lay exhausted, with beads of perspiration on the face and extremities. In all the earlier attacks and the minor attacks during the course of the disease, unconsciousness was not complete and the other symptoms were not as marked. We are indebted to Dr. Arthur D. Hirschfelder, who saw the patient with us several times and took some interesting pulse tracings. The one reproduced (Fig. 1) in this article was taken Jan. 12, 1908, one week after the onset of this series of attacks. While Dr. Hirschfelder was taking tracings that day, the patient had several seizures with syncope and convulsive movements. The accompanying record was taken shortly after these attacks and shows a brief stoppage of the ventricles without any other associated phenomena. The tracing shows distinctly the acceleration of the auricular beat with a diminished contraction, a condition which usually precedes a ventricular pause. During the stage in which the auricular impulse was feeble, the ventricles contracted independently of the auricles, causing complete heart-block. Finally, when the auricular rhythm became more regular and the force of the contraction stronger, it will be observed that every other beat stimulates the ventricles to contraction, thus producing a 2:1 rhythm.

Subsequent Course.—After the syncopal attacks subsided, the ventricles continued to beat independently, and the patient enjoyed comparative comfort. The pulse ranging from 28 to 30 per minute, remained fairly regular, and was influenced by change of position. The patient died suddenly in bed March 5, 1908.

PATHOLOGIC STUDY.

THE ANATOMY OF THE BUNDLE OF HIS.

The anatomy of the bundle of His is carefully described by Retzer.[11] The old ideas were based on the neurogenic theory. This theory taught that the impulse of contraction came from the auricle to the ventricle and was transmitted by nerves. This was not proved by experimental work, and the later myogenic theory has been confirmed by the painstaking work of His and Retzer.

Retzer states that the myogenic theory depends primarily on the demonstration of a constant muscle connection between the auricle and ventricle. The exact position should also be shown, and it should be

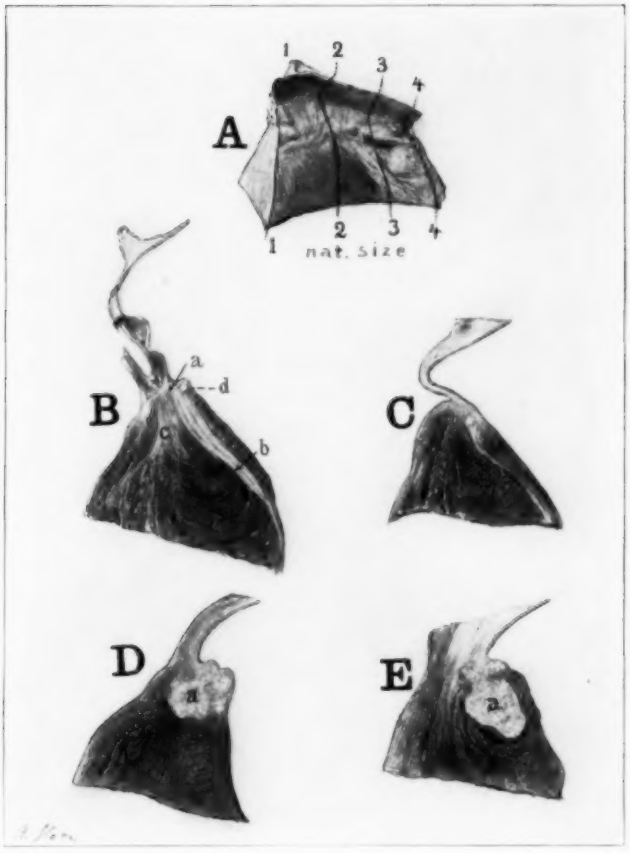

Fig. 4.—This shows a drawing of the block of heart muscle involving the ventricular septum and the fibrous auriculoventricular septum. A shows the calcareous nodule directly in the course of the bundle of His. B (which is Section 1, 1, in A) shows the branching of the bundle for the right and left ventricle; (a) indicates the position of the bundle of His in cross section between the fibrous auriculoventricular ring and the muscular portion of the ventricular septum; (b) indicates the branch for the left ventricle; (d) a calcareous nodule just above this branch; and (c), the branch for the right ventricle. C (which is Section 2, 2, in A) shows a small calcareous nodule just below the bundle of His. In D (which is Section 3, 3, in A) at (a) the irregular calcareous mass is seen to involve most of the area of the bundle of His, and in E (which is Section 4, 4, in A) at (a) the nodule is seen projecting into the region occupied by the bundle of His. (Mr. A. Horn.)

found in the lower class of animals as in the later stage of development of the human embryo.

Gaskell showed a connection between the muscle of the auricle and ventricle of the tortoise. He found a circle of muscle fibers in the fibrous ring between the auricle and the ventricle from which auricular and ventricular fibers had their origin. Kent[19] also described a muscular connection between the auricle and ventricle in such mammals as rats and rabbits.

Wilhelm His, Jr., described the auriculoventricular bundle as follows: "The muscular bundle springs from the posterior wall of the right auricle near the auricular septum in the auriculoventricular groove: it lies in the upper margin of the muscular septum of this chamber and passes forward through this until near the aorta. It then divides into a right and left limb, and the latter ends at the base of the aortic cusp.

Retzner, in a most painstaking research, has confirmed the findings of His in the main, and his examinations include the microscopic study of the hearts of cats, rabbits, rats, dogs and human beings.

Sections were cut perpendicular to the ventricular septum and parallel to the heart's axis and passing through the ventricular septum and the auricular border. Retzer was always able to demonstrate the cross-section of a muscular bundle that was sharply limited from its surroundings by connective tissue. This contrast was best brought out by Van Giesen's or Mallory's connective-tissue stain. This cross-section of what we may now call the bundle of His is found at the upper end of the septum ventriculorum directly beneath the membranous part of the septum. From the point where the bundle extends backward into the auricle, the connective tissue becomes scarcer and at last disappears, and the bundle can be no longer distinguished from the other muscle structure. From the point where the muscle is found in cross-section it also courses forward in the septum and divides into a right and left branch which send out fibers into the general muscular structure of the right and left ventricle.

On a sagittal section of the septum the bundle appears lengthwise, and the membranous portion stains blue by Mallory's stain, while beneath this the bundle of His can be seen. This bundle is not so compact as the rest of the heart muscle and contains more connective tissue. Retzer was unable to find any other muscular connection between auricles and ventricles in the auricular groove, and he thinks that he was able to exclude the presence of any other large bundle as a muscular connection.

19. Kent: Jour. Physiol., ix, 167.

By means of a lucky accident Retzer was able to demonstrate the gross anatomy of the bundle of His in the human heart. In an attempt to macerate the specimen the connective tissue of the auriculoventricular septum became so soft that the auricle separated from the ventricle and they only remained connected by the thin bundle of His.

This bundle, when viewed macroscopically from the left side of the heart, lies directly above the muscular septum of the ventricle and underneath the membranous portion of the septum. This bundle can often be seen as a delicate strand if the septum is held to the light. The bundle can be traced backward only to the right fibrous trigonum, but forward one can trace the bundle into the muscle of the ventricles. On the right side of the heart the bundle lies under the medial leaflet of the tricuspid valve, and this valve must be cut away in order that the bundle may be seen, and the endocardium must also be dissected from the auricles to the septum. After removing the muscular portion of the septum the bundle is then seen in the auriculoventricular junction where it spreads out into the musculature of the right auricle.

It may be seen, therefore, as fibers arising in the right auricle passing backward immediately above the interventricular septum, bifurcating into a right and left branch which pass down to their respective sides of the ventricle.

PATHOLOGY OF THE BUNDLE OF HIS.

Sendler,[20] in 1892, reported a case of a woman, 35 years old, who suffered for six months with fainting spells and slow pulse ranging in frequency from 24 to 37. The autopsy showed an enlarged heart. In the right ventricle 1 cm. underneath the opening of the pulmonary artery, but not involving the valve, there was a fibroma the size of a walnut. Although no microscopic sections were made, it seems that the tumor must have involved the bundle of His and produced the symptoms mentioned above.

In 1905 a case of Adams-Stokes' disease was reported by Stengel,[21] in which an atheromatous mass was found on the anterior leaflet of the mitral valve toward the base. He stated that it was over the bundle of His, where it passed from the auricle to the ventricle, but no microscopic studies were made at that time.

Schmoll[22] also described a case of Adams-Stokes' disease in which there were three or four auricular contractions to one ventricular beat.

20. Sendler: Centralbl. f. klin. Med., 1902, p. 642.
21. Stengel: Am. Jour. Med. Sc., 1905, cxxx, 1083.
22. Schmoll: Jour. Am. Med. Assn., Feb. 3, 1906, xlvi, 361.

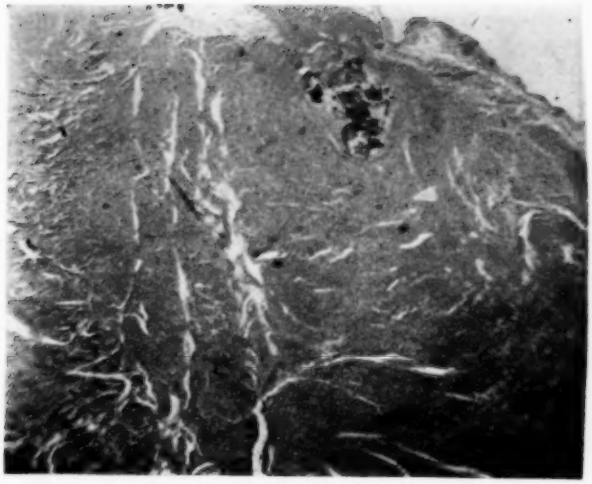

Fig. 5.—This is a color photograph of a cross section of the bundle of His which is shown at the upper part of the picture, just below the red connective tissue of the fibrous ring. To the right of this bundle and separated from it by red connective tissue is a small calcareous nodule, and running through the entire center of the picture is the longitudinal section of the branch of the bundle of His for the right ventricle. The small branch for the left ventricle is also seen beginning to the right of the calcareous nodule. These sections were made from Segment B, Figure 4, Van Giesen's connective tissue stain. (Dr. T. M. Wright.)

No macroscopic evidence of any lesions was detected, but microscopic study showed scar-formation in and around the bundle of His.

Jellick, Cooper and Ophüls[23] also reported a case of gonorrheal epididymitis in which the symptoms of Adams-Stokes' disease appeared two weeks before the patient's death. The autopsy showed an infarction in the region of the bundle of His, caused by thrombosis of the arteries, and Cooper[24] cited a case in which lesions were found in the bundle of His. Butler[25] described a similar case in which the bundle of His was infiltrated by fat to such an extent that it was atrophied to one-fifth its natural size.

Dr. Heineke[26] showed a heart at the Medical Association of Munich, June 12, 1907, from a case of Adams-Stokes' disease from which star-like gummatous myocarditis was found in the position of the bundle of His.

Hay and Moore[27] described a typical Adams-Stokes' syndrome lasting for several years in which the necropsy showed rigid and calcified coronary arteries, the right artery being almost occluded and both auricles and ventricles hypertrophied and dilated. The aorta contained a few atheromatous patches. The microscopic examination of the bundle of His showed that the central fibrous body of the bundle was an atheromatous mass, and portions of the bundle were infiltrated by many fibroblasts showing a chronic inflammation of a patchy character.

Grunbaum[28] also found a gumma in this bundle, causing typical symptoms.

Ashton, Norris and Lavenson[29] have reported a most interesting case of Adams-Stokes' disease with a complete microscopic study of the sections obtained at the autopsy. This patient had all the cardinal symptoms, including the attacks of vertigo with unconsciousness, bradycardia and incoordination of the auricles and ventricles. After numerous attacks occurring at intervals during one month the patient died, and autopsy showed a slightly hypertrophied heart, chronic passive congestion of the viscera, and a gumma of the heart involving the bundle of His. This large gummatous mass was found directly below the posterior

23. Jellick, Cooper and Ophüls: Jour. Am. Med. Assn., March 31, 1906, xlvi, 955.
24. Cooper: Jour. Am. Med. Assn., July 28, 1906, xlvii, 302.
25. Butler: Am. Jour. Med. Sc., May, 1907.
26. Heineke: Berl. klin. Wchnschr., Sept. 2, 1907, p. 1125.
27. Hay and Moore: Lancet, London, Nov. 10, 1906, clxxi, 1271.
28. Grunbaum: Progr. Med., September, 1906, p. 75.
29. Ashton, Norris and Lavenson: Am. Jour. Med. Sc., January, 1907, cxxxii, 28.

aortic cusp and passed entirely through the uppermost portion of the interventricular septum causing a projecting mass in the right ventricles, just beneath the middle tricuspid leaflet. It will thus be seen that this gumma passed completely through the area occupied by the auriculoventricular bundle. Sections through the ventricular septum perpendicular to the long axis of the heart showed that the bundle of His was completely cut in two by the gummatous process, just after the bundle left the interauricular septum and entered the ventricular septum below its membraneous or fibrous portion.

Fahr[30] has reported two cases of Adams-Stokes' disease. In one of his cases he found a mass of connective tissue forming a scar which completely cut through the left branch of the bundle of His just as it divides in order to run in the upper layers of the left ventricle. In the other case the microscopic examination revealed a gumma just as it makes its exit from the annulus fibrosus between the auricles and ventricles.

AUTOPSY REPORTS.

HEART MEASUREMENTS.

An autopsy was made about two hours after death, but the heart was the only organ that could be removed. The liver and lungs showed no evidence of chronic passive congestion. The heart on removal was found slightly enlarged, weighing 450 grams. Measurements:

1. Just above the aortic valve, 8.5 cm.
2. Length of left ventricle, including muscle, 8.5 cm.
3. Thickness of left ventricle midway, 21 mm.
4. Mitral valve, 10 cm.
5. Pulmonary valve, 8 cm.
6. Length of right ventricle, 10 cm.
7. Thickness of right ventricle, 6 cm.
8. Tricuspid valve stretched, 14 cm.

NEW GROWTHS WITHIN THE HEART.

On opening up the left side of the heart, a calcareous projecting nodule was found, measuring about 9 mm. in diameter and extending from 6 to 9 mm. out into the chamber of the ventricle. The mass was somewhat irregular in shape and of a yellow color. It was about 2 cm. immediately below the mesial aortic cusp and ran backward along the upper portion of the ventricular septum, following the course of the coronary artery and involving also the attachment of the anterior leaflet of the mitral valve. An irregular projection of this mass also passed through just beneath the endocardium in a position corresponding to the junction of the muscular portion of the ventricular septum with the membranous portion of the septum. This mass projected forward in the upper portion of the septum for a distance of 12 mm. from the base of the original calcareous mass and occupied therefore the position of a portion of the bundle of His as it passed through the ventricular septum before dividing into the branches for the left and right ventricles. This mass, therefore, extended for about 1 cm. in the position of the bundle of His and ended about where the bundle divided

30. Fahr: Virchow's Arch. f. Path. Anat., 1907, clxxxviii, 562.

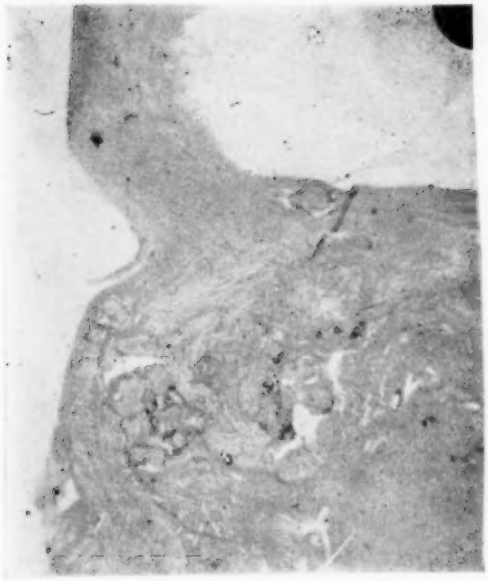

Fig. 6.—To the left of the picture is seen the fibrous auricular septum branching into the auriculoventricular fibrous septum. Below this, in about the center of the picture is the small yellow band of muscle fibers of the bundle of His. Above this bundle and to the right of it, almost completely surrounding it is the calcareous nodule pressing on it in several directions. Beyond this to the right is the normal heart muscle. These sections were made from Segment C, Figure 4. (Dr. T. M. Wright.)

into its two ventricular branches. It must have interrupted the impulse from the auricles to the ventricles conveyed through the bundle of His.

There was another smaller calcareous nodule just at the posterior aortic cusp. This cusp was slightly shrunken and calcareous and there are a few atheromatous patches in the aorta.

CORONARY ARTERIES.

The transverse branch of the left coronary artery was completely calcareous; for a distance of 4.5 cm. it forms a rigid tube, but its lumen was not completely obliterated as it admitted a probe of a little less than 1 mm. in diameter.

The descending branch was not completely calcareous, but it was thickened and comparatively rigid for a distance of 3.5 cm. as it descended to the apex. It would also allow the passage of the probe mentioned above.

About 4 cm. from the origin of the aorta the right coronary artery was firm, bony and rigid for a distance of 1.8 cm. This ended just as it divides into the descending and transverse branch and the transverse branch continued as a thickened tube, while the descending branch was very tortuous.

The main branch of the right coronary artery from its origin to the rigid portion was simply thickened. The color photograph, or Figure 2, shows the calcareous mass projecting from the base of the mitral valve, projections from which invaded the area of the bundle of His.

MICROSCOPIC EXAMINATION.

For the purpose of microscopic examination a block of the heart tissue was cut from the specimen which involved practically the entire course of the bundle of His through and beneath the auriculoventricular septum, which also included its branches for the left and right ventricles.

The photograph seen in Figure 3 will show this block of tissue as viewed from the left ventricle. In this plane it is seen to include the endocardium covering the left ventricle at the extreme upper portion of the ventricular septum and also the annulus fibrosus or auriculoventricular fibrous ring above.

This block was divided into three portions, which are represented in Figure 4, called, respectively, Segments 1, 2, 3, from the numbers at the upper plane of each segment. Each of these planes is represented by an irregular figure, (B, C, D, E, Fig. 4), resembling a triangle whose sides are formed by the endocardium of the right and left ventricles, and whose apex is the upper end of the fibrous auriculoventricular septum.

The original block at the upper portion of the plate shows the endocardial surface of the left ventricle, and the irregular nodules of calcareous material are well indicated as projecting out into the cavity of the left ventricle, and causing irregular projections of the endocardium. It can also be noted that the calcareous material really forms an irregular column which runs from right to left just where the auriculoventricular fibrous septum joins the ventricular septum forming a groove for the bundle of His, and this can be verified by examining the segments of the original block by means of a small hand lens. This appearance is indicated by Sections B, C, D, E in Figure 4, which show cross-sections of the ventricular septum ending in the apex formed by the fibrous auriculoventricular septum. At *a* in Figure 4, B, the bundle of His is seen branching from each ventricle, the long strip *b* forming the branch for the left ventricle. This is just beneath the endocarium, while the branch for the right ventricle *c* is deeper down beneath the surface of the right ventricle. Although this portion of the bundle is farthest away from the calcareous nodule at the base of the mitral valve (Fig. 3, B), yet the column of calcareous material has extended along the course of the bundle as far as this point, and a small point

of this material can be seen at D. This touches the upper part of the left branch, but probably this did not exert any pressure on the bundle of His at this point, whereas the deposit nearer the original source of the calcareous material not only pressed on the bundle, but apparently in places almost entirely replaced it.

The direction and situation of Segment 2 (Fig. 4, A) is indicated in the original block labeled natural size by the dotted lines marked 2-2. On viewing this on cross-section as C, Figure 4, a small nodule is seen to the right and below the bundle, but in Segment 3 (Fig. 4, D) the entire region of the bundle of His at *a* is involved in the deposit of lime salts. The plane of this section is seen at the dotted lines 3-3 in the original blocks.

In E, Figure 4, the mass of lime salts is even larger, and in both of these situations it will be seen from future studies of microscopic sections that the pressure exerted by the deposits produced atrophy, fibrosis and in one place almost a complete obliteration of the bundle of His. This plate (Fig. 4) in itself shows very clearly how the lesion must have interfered with the normal course of impulses from the auricles to the ventricles.

DESCRIPTION OF MICROSCOPIC SECTIONS.

Serial sections were cut from three different places in each of these segments. Figure 4, B, C, D, E, show the plane representing the directions of the sections and they can be seen, therefore, to pass through the junction of the upper part of the interventricular septum with the annulus fibrosus or fibrous ring between the auricles and ventricles. Since the bundle of His passes directly through this junction, transverse sections were made through the bundle of His throughout its entire extent until the bundle branched for the right and left ventricles; oblique and longitudinal sections were, of course, made through this latter area of branching.

Section D (Fig. 4) was made from Segment 3 at a point farthest from the branching of the bundle and nearest, therefore, to Point B seen in Figure 3, the photograph of the gross specimen.

The entire area occupied by the bundle of His was infiltrated by a calcareous material, a portion of which stained blue with hematoxylin. At first sight it would appear that the entire bundle of His had been obliterated, but on closer inspection there was found a narrow strip of muscular tissue surrounded on all sides by calcareous infiltration or newly formed fibrous tissue.

This mass was about 0.05 of an inch long and about 0.01 of an inch in width as measured by the micrometer scale, whereas the normal bundle is 0.1 of an inch in diameter.

In other sections from this same segment the strip measured only 0.03 of an inch in length, but was apparent in all sections from this end of the segment.

A second set of sections was cut from the middle portion of this segment, No. 3, and in some of these sections the bundle showed great atrophy. This measured 0.04 of an inch in longitudinal direction, but was 0.025 of an inch in cross diameter. It contained a few strips of newly formed fibrous tissue, showing typical fibrous myocarditis.

In other sections cut from this part of Segment 3 the thin strip of the bundle of His appeared in about the center of the calcareous area; it was 0.05 of an inch in length and 0.02 of an inch in thickness. In other sections cut from this same block the bundle of His at first sight seemed to have entirely disappeared, but on further examination small groups of cells were found which seemed to be mere remnants of the atrophic bundle of His. Many of these resembled connective-tissue cells, while others, when examined with the immersion

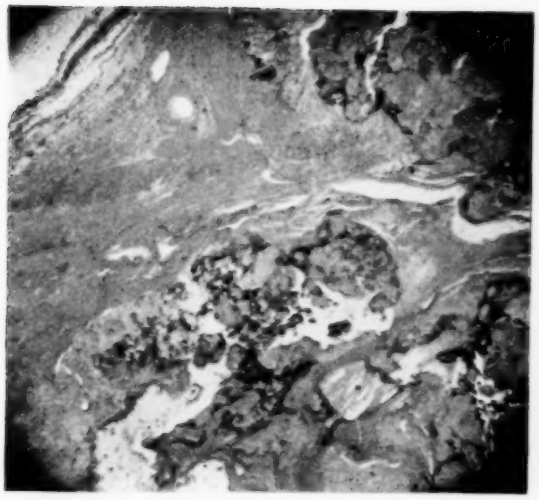

Fig. 7.—To the left and above is the red connective tissue of the fibrous ring, and in the center of the picture is the small atrophic band of yellow muscle fibers of the bundle of His. It is surrounded on all sides by calcareous material and also shows marked fibrous myocarditis, as indicated by the red bands of connective tissue. This section was made from the Segment D, Figure 4. (Dr. T. M. Wright.)

Fig. 8.—This shows the bundle of His in the center of the picture as yellow muscle fibers. It is invaded by the red bands of connective tissue, and surrounded on all sides by calcareous material. (Dr. T. M. Wright.)

lens, showed the large nucleus of the heart-muscle fiber surrounded by the fibrillar protoplasm of the heart muscle.

In the sections from that part of Segment 3 nearest to the branches to the ventricles the thin strip of the bundle of His measured 0.07 of an inch in length and 0.02 of an inch in width; in other sections from this same area the bundle only remained as thin atrophic bands of muscle fibers surrounded by thick strands of connective tissue. These muscle fibers had almost completely lost their cross-striations, but were probably able to preserve the continuity of the bundle.

In Segment C, Figure 4, cut as the central block of the three portions, into which the original block of segments was divided, somewhat different conditions were noted. In sections taken from that portion of the block furthest away from the branching of the bundle of His for the ventricles the calcareous infiltration around the bundle of His was much smaller in area, and it had not invaded the bundle. One small calcareous mass was found on either side of the bundle between the fibrous tissue capsule and the endocardium of the right and left ventricle respectively. The bundle itself is surrounded by a thick connective tissue, sending numerous branches in between the muscular bundles themselves. The bundle in this region measured 0.02 of an inch in the direction from the auricle to the ventricle or from base to apex; in the direction from the right to the left ventricle it measured 0.08 of an inch.

In sections which were made from the middle of Segment 2 the bundle measured 0.03 of an inch from apex to base and 0.08 of an inch from ventricle to ventricle. There were two small calcareous areas in the connective tissue surrounding the bundle and a very small one in the fibrous auriculoventricular septum, but there was no evidence of pressure on the bundle itself by these masses.

In sections made from that part of Segment 2 nearest the branching of the bundle for the ventricles, the bundle of His again became smaller, while the calcareous deposits were much larger; in places these had entirely replaced the connective tissue capsule which separated the bundle from the ventricular septum. They had even invaded the bundle at its periphery and they must have produced pressure on this structure; the bundle measured 0.015 of an inch in a direction from base toward apex and 0.06 of an inch in a direction from ventricle to ventricle. In other sections from this same area the atrophy of the bundle was even more pronounced, for it measured only 0.01 of an inch from base to apex. The changes in the bundle of His itself which were seen when examined under the high power were certainly produced by the pressure of the calcareous material on the bundle; this had produced chronic fibrous myocarditis. When examined by Van Giesen's stain, both large and small bands of fibrous tissue were seen traversing the bundle. The muscular fibers of the bundle were narrower than normal, measuring about 0.0003 of an inch, while the muscular fibers of the regular heart muscle measures 0.001 of an inch in breadth.

The arteries in the bundle of His showed marked endarteritis; the calcareous material surrounding the bundle was typical, and this was surrounded by a thick fibrous capsule with very few fibroblasts, but in certain areas there were numerous densely packed fibroblasts forming small groups; in places these were more loosely packed, giving the tissue a myxomatous appearance.

In certain portions of the bundle made from Segment 2 there were groups of fibroblasts and a few fat cells. The smaller strands of connective tissue could often be seen surrounding individual muscle fibers producing marked atrophy.

The sections from Segment 1 showed the bundle after it had branched from the right and left ventricle; these branches showed some fibrous myocarditis and a newly formed fibrous tissue at times containing fine granular deposits of lime

salts. The perinuclear spaces of the muscle fibers showed numerous fine light brown granules characteristic of brown atrophy.

GENERAL CONDITION OF HEART MUSCLE.

Sections were examined from several portions of both auricles and ventricles, but with the exception of marked brown atrophy and shriveling of the nuclei of the heart muscle no other changes were noticed. Sections from the coronary artery or its branches showed marked chronic fibrous endarteritis, in places the intima being twice as thick as the media. Whether the death of the patient was produced by the disease in the bundle of His or by coronary artery disease or both is difficult to say.

CONCLUSIONS.

From what has been said it can be seen that the primary lesion in this case consisted in marked calcareous infiltration of the auriculoventricular groove and its surrounding muscular and fibrous tissue. This produced pressure on the bundle of His, causing extensive fibrous myocarditis with atrophy of the muscular fibers. These conditions must have interfered with the normal transmission of the muscular impulse from the auricles to the ventricles, thus producing the symptoms described in the paper.

We desire to thank Drs. Retzer and Hirschfelder for their interest in this case, and Prof. T. W. Simon and Dr. T. M. Wright for the color photographs illustrating this article.

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TRICUSPID STENOSIS, WITH REPORT OF A CURE.

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Among the hundred and eighty-seven cases of tricuspid stenosis found in the literature in but ten cases was a correct diagnosis made clinically. In view of this fact it seems worth while to record such a case in which the clinical diagnosis was confirmed at autopsy.

Patient.—A housewife, aged 35.

History.—The patient's father died of heart disease. The patient had measles, mumps, pertussis, scarlatina, diphtheria twice, and smallpox, all in childhood; at 10 and 27 acute articular rheumatism, involving knees, ankles and wrists.

Onset of Present Illness.—The patient was first admitted to St. Luke's Hospital, April 20, 1905, giving history of shortness of breath, palpitation and observed irregularity of heart during the past four years. Three years before admission the abdomen began to swell and was first tapped one year later. Tapping was repeated four months, and again six weeks before entering the hospital. The only complaint throughout this period was shortness of breath "when the abdomen was swollen."

First Physical Examination (April, 1905).—Heart: Apex in fifth space, 4½ inches to the left of mid-sternum. Right border 2½ inches from mid-sternum in third space. Action regular. First apical sound loud; second pulmonic, not accentuated. Second aortic inaudible. At mitral area, and, transmitted to the left, a blowing systolic murmur. At aortic area a pronounced systolic thrill and a double murmur, a systolic, loud and harsh in quality, transmitted upward and heard in vessels of neck, also over greater part of anterior chest, and, posteriorly, between scapulæ; a blowing diastolic transmitted down left border of sternum.

Pulse: Small, regular, moderate force. Veins of neck distended; pulsation not remarked. Systolic arterial pressure 120 mm.

Chest: Small fluid accumulation at both bases.

Abdomen: Enormously distended, signs being those of large amount of fluid.

Extremities: Edematous, indurated, pigmented; superficial veins dilated.

Following aspiration of 592 ounces of fluid from peritoneal cavity, friction fremitus was noted over liver, edge of which was palpable three inches below costal border.

Remission.—Improvement was rapid; the patient left the hospital and was not heard from until over two years later. In August, 1907, she was readmitted complaining of edema, dyspnea and weakness.

Second Physical Examination (August, 1907).—Heart: Apex in fifth space, 4½ inches to left of mid-sternum. Action irregular, intermittent, poor force. At apex a rumbling presystolic murmur and blowing systolic murmur, a loud first sound. At aortic area a double murmur, a systolic of rough, intense quality transmitted upward, heard in vessels of neck and a diastolic referred down sternum and also heard in second and third left interspaces. In fourth and fifth spaces to right of sternum a soft, blowing systolic of very different quality from

apical murmur of same phase, and a snapping, valvular second sound. Right border 2 inches from mid-sternum in third interspace. Epigastric pulsation marked. Veins of neck widely distended, but without visible pulsation.

Pulse: Irregular, small, of poor force; tension 105 mm.

Moderate effusion in right pleural space.

Abdomen: Circumference 62 inches, symmetrical, tense, showing distinct signs of fluid.

Extremities: Markedly edematous, excoriated, ulcerating.

Clinical Course.—Rest in bed, abdominal paracentesis, digitalis and morphin, as the only therapeutic measures, enabled the patient to sit in a chair after twelve days and she was soon walking about the ward. In the interval from August 26 to November 16, the abdomen was tapped eleven times and a total of 3,665 ounces of fluid removed. There was constant diffuse cyanosis of the entire body, but slight edema of the extremities after the first week, and little or no dyspnea, except when the abdomen became greatly distended with fluid. Leaving the hospital November, 1907, the patient continued in comfort until March, 1908, when ascites compelled her return. The cardiac signs were the same as previously, except that a diastolic murmur of quality thought to be different from that heard at the aortic area was noted at the ensiform.

Diagnosis.—Aortic stenosis and insufficiency with mitral insufficiency had been the most frequent diagnosis during the patient's stay in the hospital. The presence of a tricuspid stenosis suggested itself to me in 1907, and was affirmed positively and independently by Dr. Van Horne Norrie, on whose service the patient came to autopsy, and by whose courtesy I am able to publish this report.

Autopsy.—The patient died April 30, 1908. The autopsy, by Dr. Zinsser, showed:

Heart: Apex in seventh space, 4½ inches to left of mid-sternum. Right border ¾ inch to right of right sternal margin. Pericardial sac totally obliterated by very firm adhesive pericarditis. Right auricle and ventricle much dilated, walls flabby and thin. Tricuspid valve segments much thickened, adherent at angles, forming a firm ring about auriculoventricular opening, which admitted with difficulty tips of two fingers, and forming distinct stenosis. Pulmonary valves normal. Left ventricle greatly hypertrophied showing interstitial myocarditis. Aortic valve adherent; marked thickening of valve segments with resultant button hole stenosis. Mitral valve with funnel stenosis admitting one finger. No fresh vegetations on endocardium.

Left pleural cavity: Large amount of fluid. Left lung thickened, atelectatic, compressed to one-fifth normal volume.

Right lung: With adhesive pleurisy of long standing.

Abdomen: Peritoneum universally thickened, in areas showing fibrinous exudate.

Liver: Weight, 2,890 gm., marked perihepatitis (Zuckergussleber), chronic congestion, cirrhosis of pronounced degree.

Spleen: Very large, marked perisplenitis.

Kidneys: Large, soft, congested.

To become convinced that tricuspid stenosis is not a rare lesion one has to review the observations of the many who have described the condition since Duroziez, in 1868, first brought it convincingly to notice. The subjective and objective evidences of the condition have been in the course of time formulated until a fairly definite clinical picture may be drawn. This has been well done by J. B. Herrick.

The case reported well illustrates the important features of the condition: A woman having a history of acute articular rheumatism or chorea, prominent among whose symptoms are persistent cyanosis of mucous membranes and skin, marked tendency to edema or general anasarca and with relatively little dyspnea; the signs of a mitral stenosis without accentuation of the second pulmonic sound, often, in addition, an aortic lesion, an enlarged right ventricle and auricle, distended veins of the neck, frequently without pulsation. These comprise the most constant diagnostic factors. To them may be added Mackenzie's observation that seven of these cases proved at autopsy showed a liver pulse of the auricular type. The murmur is very inconstant and more often absent than present. In fact, very few of the cases carefully observed and recorded have shown the presystolic murmur to the right of the sternum so insisted on by many. As a positive sign such a murmur is confirmatory, but negatively has no weight in the diagnosis. All auscultatory signs are so often obscured by the presence of lesion of the mitral and perhaps aortic valves that very great weight can not safely be placed on them.

The remarkable comfort of these patients in the presence of cyanosis and, frequently, edema or general anasarca, has been very often noted. This is doubtless due to the effect of the narrowed right auriculoventricular orifice lessening the engorgement of the pulmonary circulation and the consequent dyspnea. This same factor, by its tendency to equalize pressure on either side of the pulmonary valve, furnishes a satisfactory explanation for the frequent absence of accentuation of the second pulmonic sound in the presence of the almost universally accompanying stenosis of the mitral valve.

In Steele's collection of reports of eighty-six cases a chronic obliterating pericarditis was present in seven. Broadbent, Kassen Beck, Cochs and Chadbourne also record one each. These, together with the case here reported, make a total of twelve showing this condition.

Duroziez in 1868, Leudet in 1888 and J. B. Herrick in 1897 have summarized the cases of tricuspid stenosis, the last-named tabulating one hundred and fifty-four. In reviewing subsequent literature I have found reports, complete or incomplete, of thirty-three additional cases. These include eight collected by Satterthwaite in 1902.

SUMMARY OF REPORTED CASES TO DATE.

Sex.—		Age.—	
Male	38	10 to 20 years	16
Female	133	20 to 30 years	59
Sex not known	16	30 to 40 years	38
		40 to 50 years	28
Previous History.—		50 to 60 years	10
Rheumatism	61	60 to 70 years	6
Doubtful rheumatism or chorea	11	Not known	30
No rheumatism	33		
Not known	82	Total cases	187

Association of Valvular Lesions.—	
Tricuspid alone	14
Tricuspid and mitral	102
Tricuspid and aortic	64
Tricuspid and aortic and pulmonary	1
Tricuspid and endocardium of left auricle	1
Tricuspid mitral and pulmonary	2
Total cases	187
Cases showing adherent pericardium	12

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THE INHIBITION OF PANCREATIC ACTIVITY BY EXTRACTS OF SUPRARENAL AND PITUITARY BODIES.

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(From the Pepper Laboratory of Clinical Medicine and the Laboratory of Experimental Surgery, University of Pennsylvania.)

The accompanying records are illustrative of the article by the present authors on "The Inhibition of Pancreatic Activity by Extracts of Suprarenal and Pituitary Bodies," appearing in the ARCHIVES OF INTERNAL MEDICINE, Vol. I, No. 6, July, 1908, pages 628-647. They show the inhibitory effects of the intravenous injection of extracts of the suprarenal and pituitary bodies into dogs whose pancreatic juice has been excited by secretin.

It is to be regretted that it is impossible to reproduce more of the records, especially those which illustrate the prevention of excitation of pancreatic flow when the dose of secretin is preceded by an injection of suprarenal or pituitary extract. Under these circumstances the inhibition is more marked, but its proper exposition requires the consideration of a number of lengthy control records whose publication is impracticable. This is also true of those records which illustrate the inhibitory factor of suprarenal extracts as something apart from the effect on blood pressure. The reproduction of still other features is omitted for the same reason.

In the accompanying chart the upper line in each series of tracings represents the respiration as recorded by a manometer in the trachea; the next line represents the blood presssure as recorded by a manometer in the femoral artery; the line next to the lowest marks the time in seconds, and the lowest line records the injection of secretin and the in-

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[Through an oversight on the part of the Editor, the charts which accompanied article by Drs. Pemberton and Sweet (ARCHIVES, vol. i, No. 6) were omitted. They are here inclosed as a supplement.—EDITOR.]

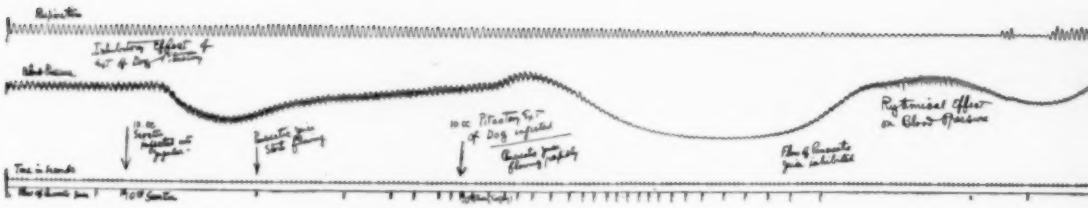
jection of extracts, both of which are marked by a triple interruption of its continuity. This line also marks the flow of pancreatic juice, each isolated interruption indicating the flow of the juice past a division marked on a glass canula introduced into the pancreatic duct.

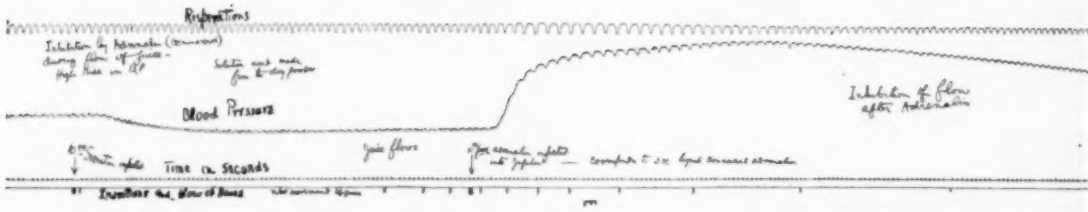
It should be stated for a proper understanding of the records that the normal response to the given dose of secretin is a prolonged flow of pancreatic juice, lasting sometimes many minutes, in contrast to which the accompanying records of flow show a distinct slowing and early cessation. Space will not permit of the reproduction of such a lengthy tracing as the normal.

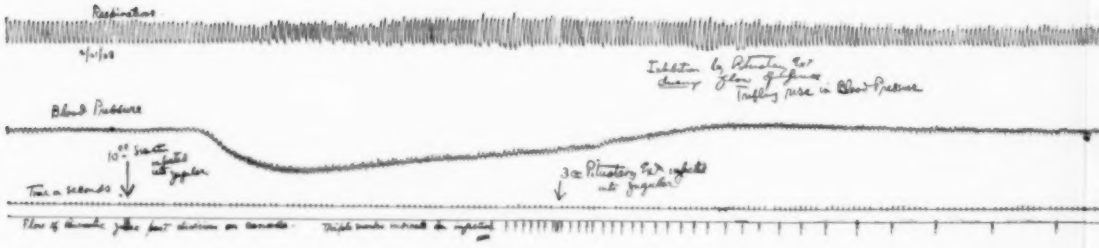
The upper series of tracings shows the stoppage of pancreatic flow by an extract of the pituitary body of dogs, with a coincident high rise in blood pressure.

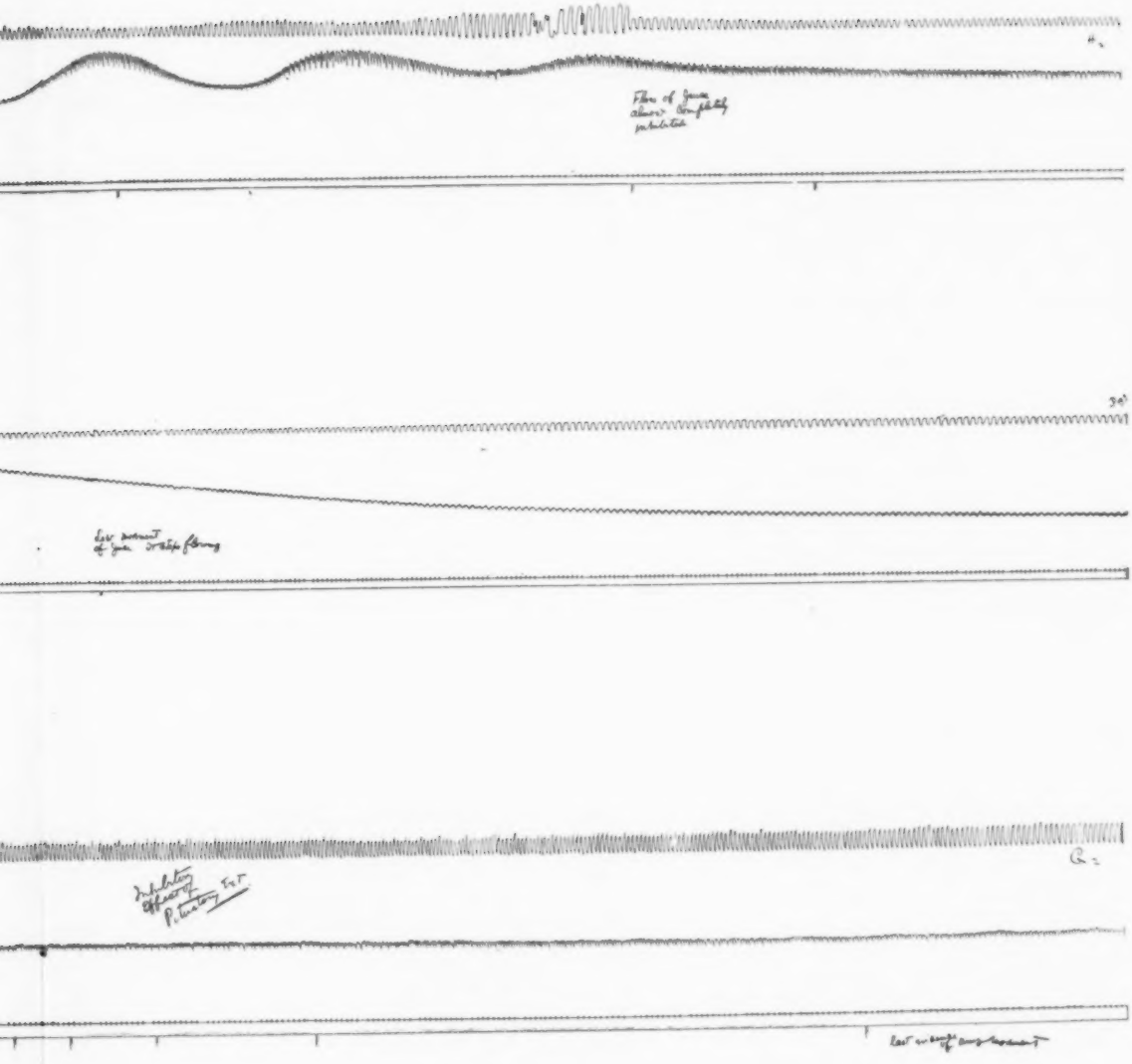
The middle series shows the same following an injection of adrenalin.

The lowest series shows the inhibitory effect following an injection of pituitary extract with a very slight rise in blood pressure.


Respiration
Inhibitory Effect of
Blood Pressure
Time in Seconds


Respirations
Inhibition by Adrenalin (terminal)
Blood Pressure
Time in Seconds


Respiration
Blood Pressure
Time in Seconds



THE TREATMENT OF THYROIDISM BY A SPECIFIC CYTOTOXIC SERUM.*

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NEW YORK.

During the past two years a large number of cases of hyperthyroidism have been treated with a specific serum.[1] Preliminary papers[2] have been published dealing with the preparation of the serum and the therapeutic results obtained by its use. In the present paper we propose to discuss the questions arising from this study from the standpoint of accumulated experience and it is hoped to make the method so plain that any physician may understand the rationale of the treatment and the special points to be observed in its application. There are two fundamental propositions to be considered, viz., the nature of the serum and the nature of the disease. These will be considered in order.

THE SERUM.

We have called the serum which we have used specific because we believe that it has a special action on the thyroid gland, and it is necessary for the argument that the grounds for such belief should be reviewed. It is now a well-known and universally admitted fact that the proteid of each animal species has a characteristic physicochemical structure; in other words, it is specific. The chemical methods by which differences in structure are determined have not as yet been refined to a sufficient extent to render it possible to make a chemical distinction between proteids from closely related species of animals, but the methods employed in immunity investigations of the last few years have been thus refined and their reliability has been demonstrated in such degree that the results obtained by these methods are accepted by most investigators as demonstrating specific characters of the proteid in each animal species. This specificity is not absolute, for it has been found that a

*This article represents the Mütter Lecture which was delivered before the College of Physicians in Philadelphia, Dec. 13, 1907.

1. It will be recalled that the serum to which we refer is made by inoculating animals (rabbits or sheep), with the pure proteids from the human thyroid gland. In the beginning the proteids were obtained only from goitrous glands, but more recently the proteids from normal glands have been used successfully.

2. Beebe, S. P.: Preparation of a Serum for the Treatment of Exophthalmic Goiter, Jour. Am. Med. Assn., 1906, xliv, 487. Beebe: Tr. Assn. Am. Phys., 1906, p. 548. Rogers, John: The Treatment of Thyroidism by a Specific Serum, Jour. Am. Med. Assn., 1906, xlvii, 655.

serum made against the proteid of a given species will show a mild reaction against the serum from closely related species, but by observing the time and the dilution in which the reaction takes place it is possible to distinguish sharply between species. Heterologous proteids, that is, proteids from different species, may be readily separated by means of these serum reactions, and it seemed to us reasonable to believe that a method capable of making such fine distinctions would enable one to differentiate between homologous proteids, that is, between proteids taken from the different organs of the same species. The widely varying functions of the different organs are dependent on the physicochemical structure of the various cells which compose them, and it would seem there must exist sufficient individuality of structure in organs which have such widely varying functions as the liver and kidney to permit of its recognition by the highly selective biologic method. One of the most suggestive researches in this line was that of Uhlenhuth,[3] who found it possible to differentiate sharply between the proteids in the white and yolk of the egg by means of a serum made against one or the other of these proteids. He found that it was possible to get a mild reaction to the proteids of the yolk by means of serum developed against the proteids of the white of the egg, but only slowly, even in high concentrations of serum, so that in point of time and in delicacy the reactions of these homologous proteids against their own serum was specific.

If the serum is developed by injecting the pulp of an organ into some alien species of animal, we shall develop anti-bodies against all the proteids so introduced, and it is obvious that such a serum must contain a number of factors. Certain of these may be specific, since they are developed against the proteid which is found only in the particular organ in question, while others, such as those developed against the blood, must be common. A very large number of experiments are now on record which support such a conclusion, but in many of them the specific action is so obscured by the common action that its demonstration has not always been satisfactory. In a paper published three years ago by one of us[4] this question was discussed and the reasons were given for choosing certain pure proteids—viz., the nucleoproteids—from organs as nearly blood-free as practicable, for developing specific antiserum. Reasons were given in that paper for believing that relatively more of

3. Uhlenhuth: Zur Lehre von der Unterscheidung verschiedener Eiweissarten mit Hilfe specifischen Sera. Festschift, Geburtstag von Rob. Koch, Jena, 1903, p. 49.

4. Beebe, S. P.: Cytotoxic Serum Produced by the Injection of Nucleoproteids, Jour. Exper. Med., vii, 733.

the specific factors and less of the common element were produced than by including the whole organ pulp in the injected material. The specific action of such serum has been determined by the precipitin test, the agglutinin test, and by injection of the serum *in vivo*. The precipitin test is well known. The agglutinin test is similar to that employed in bacterial reactions, except that a suspension of finely divided tissue fragments is substituted for the bacterial emulsion. Such reactions *in vitro* show that homologous proteids may be differentiated sharply from one another. In point of time and in completeness of the reaction the serum is specific. When introduced into the body the reactions are specific in the sense that severe lesions can be produced in the selected organ without causing a corresponding lesion in other organs.

The serum has at least two factors: first, the factor common to proteids of all the organs of the body, and to a lesser degree the proteids of closely related species; second, the specific factor acting on one particular organ. We have found it possible to demonstrate these two factors by means of absorption experiments. If we inject dog-kidney nucleoproteids into a rabbit we produce a serum which gives a mild reaction with dog serum, also with proteids from the dog's liver or other organs, but a very marked reaction with kidney proteids. If we now add to this serum a considerable quantity of dog-liver tissue ground to fine hash and allow the two to stand in contact for a few hours in the refrigerator, and then filter, first through paper, and later through a Berkefield candle, we find that the common factor of the serum has been removed.[5] Such serum no longer has any precipitating or agglutinating effect on liver proteids or suspension of liver tissue fragments, nor does it act on any other proteids except those from the kidneys, and on the latter its action, although very marked, is somewhat less than before the absorption. By the addition of a large number of washed erythrocytes, one may also absorb the common factor. Such absorbed serum will cause kidney lesions when injected intravenously into the dog's circulation. If, however, one absorbs the kidney serum with kidney tissues one finds that the specific factors and the common factors have both been removed.[6]

The serum which has just been described was made from organs containing a small amount of blood, and one of the criticisms which has been made of this work is based on the fact that the serum itself is slightly hemagglutinative and hemolytic. The lesions found in the body after the injection of such serum are explained by these critics (Pearce

5. The liver tissues used for this purpose were not blood-free.
6. Beebe, S. P.: Nucleoproteid Immunity, Brit. Med. Jour. 1906, p. 1786.

and Jackson[7]) by assuming that the serum has caused the formation of small emboli of erythrocytes and that the resulting thrombi have caused anemic necroses. The lesions which we found, however, were not of that type, and moreover, they were produced also by serum from which hemolytic factors had first been absorbed in the manner described above; we conclude, therefore, that they have been produced by a special organ cytotoxin. We have some corroborative evidence that the hemolysins are not actively concerned in producing the lesions, viz., the plain unabsorbed serum is slightly hemolytic *in vitro,* and yet when injected into an animal it invariably was followed in a few hours by the presence of an increased number of red cells in the blood and at the same time a severe lesion was being produced in some specific organ. We have in such findings no evidence of blood destruction.

We have reviewed the principles of the serum at this length because it is of fundamental importance that we establish reasons for believing that serum made from the thyroid gland has a special action on that gland; for obviously if the serum acts as much on the kidneys, the liver, or the intestinal epithelium as it does on the thyroid, we have no logical ground or excuse for using it in the treatment of disease of the thyroid gland.

The methods followed in the making of the serum have been described in a previous article[1] and no essential change has been made during the last year.[8] We are not yet fully acquainted with the differences between

7. Pearce and Jackson: Concerning the Production of Cytoxic Sera by the Injection of Nucleoproteids, Jour. Infect. Dis., 1906, iii, p. 742.

8. The various steps in the production of this serum are briefly as follows: The fresh, human thyroid glands, which must not be preserved in formalin, or alcohol, or any substance which coagulates the albumin, are ground to a very fine pulp and extracted in several times their volume of salt solution made faintly alkalin with sodium hydroxid. Extraction is carried on in a refrigerator for twenty-four to thirty-six hours, and chloroform or thymol may be added to prevent bacterial growth. The coarser particles in the extract are then removed by straining through gauze, the filtrate centrifugated and filtered through paper. A clear extract may be readily obtained by filtering the strained extract through a Buchner funnel filled with paper pulp. We have found that a very convenient method for precipitating the proteids from this extract is to acidify with acetic acid to a concentration of 0.1 per cent., add a sufficient amount of saturated sodium chlorid solution to make the concentration of the salt in the extract 10 per cent. of saturation, and then heat to 44 degrees C. for half an hour. Under these conditions we obtain an abundant flocculent precipitate which may be readily washed, redissolved by the addition of a small amount of alkali and reprecipitated by the addition of acetic acid. The proteid is redissolved and reprecipitated three times, and is thoroughly washed each time. The purified proteid is dissolved in alkaline salt solution for inoculation into the peritoneal cavity of the rabbit or sheep in which we develop the serum. From five to eight inoculations one week apart are given to each animal before the blood is withdrawn and the serum prepared in the usual method.

a serum made from the nucleoproteid and that from the nucleoproteid and globulin combined; but we are still inclined to the belief that the serum from the nucleoproteid is more cytotoxic than that from the globulin, though the latter proteid is more efficient in the development of antitoxins.

We wish again to emphasize the fact that the serum must be made from human thyroid glands, because of the biologic specificity of proteids. It would be quite as logical to use tetanus antitoxin in the treatment of diphtheria as to use a serum made against sheep thyroid in the treatment of a human subject. We can get no evidence *in vitro* that such a serum has any antagonistic action against the human thyroid proteids. On this ground alone, therefore, the negative results which Murray[9] obtained in the use of serum made in a goat against sheep proteids are precisely what should have been expected. Our serum has been made in sheep and rabbits against the proteids of the human thyroid gland.

One never reaches a condition of immunity at all comparable with the immunity to a diffusible bacterial toxin. From three to four times the initial dose of proteid may be safely given at the end of the immunization period, but one can not go beyond this point.

Although the serum shows a high degree of antagonistic action *in vitro* it does not in the immunized animal protect against excessive doses of the specific proteid. We have, nevertheless, data from some experiments which indicate that it does have some power of conferring passive immunity. Six fresh adult rabbits were kept under observation for some days to make sure that they were in a healthy condition. One group of three was then given for two successive days 5 c.c. doses of an active thyroid antiserum previously made in other rabbits. There was no reaction because of the biologic identity of the serum. Twelve hours following the second injection of serum, all six rabbits were given large doses of human thyroid proteids. The three protected rabbits had a milder immediate reaction and the late effects, such as loss of weight, were much less marked in this group than in the non-protected group. Clinically, we see acute toxic cases in which the subjects experience very marked and quite immediate beneficial results from the injection of the antiserum, a result quite similar to what we should expect if we were neutralizing a toxic substance. Obviously we can not be so certain of our ground here as we can in a laboratory experiment in which we can control matters so as to have fewer unknown factors.

9. Murray: Lancet, London, Nov. 11, 1905.

THE DISEASE.

In our previous paper[10] we have outlined the evidence for believing the symptoms of the disease to have their origin in a condition of hyperactivity of the thyroid gland. Such a mode of origin is a fundamental premise in our treatment of these cases with an active antiserum designed to neutralize the toxic effects of thyroid proteid in the circulation, and also to inhibit the secretory activities of the gland. The symptoms of thyroid cases, tremor, nervous irritability, tachycardia, diarrhea, perspiration, rapid loss of weight, have all been produced in animals and also in the human subject by the administration of thyroid preparations. The almost constant occurrence of goiter, the histologic appearances indicative of increased activity, and the greatly increased circulation through the gland vessels, together with the amelioration of the condition by surgical removal, are additional arguments that the gland is a fundamental factor in the disease. The large relative lymphocytosis, and the diminished excretion of kreatinin with increased output of kreatin are the usual findings in the typical well-developed patient with Basedow's disease, and these blood findings have likewise been produced by the administration of thyroid preparations to healthy animals.[11] A discussion of the etiology of the disease is not within the scope of the present paper, and we accept provisionally the theory that in typical cases the characteristic symptoms have their origin mainly in the hypersecretion from the thyroid gland.

There are certain limitations to our knowledge in this matter, however, which should be pointed out. It is not known whether the physiologic activity of the gland is dependent solely on the iodized proteid therein contained, and, if so, whether the activity is measured by the quantitative amount of iodin present. As has been pointed out elsewhere, there is an increased amount of nucleoproteid[12] in the gland in Graves' disease, but this is a function of the cellular hyperplasia and we do not know whether or not it has any significance in the physiologic action of the secretion.

There is no experimental evidence to determine whether or not the secretion from the gland in Graves' disease has more or less physiologic activity than the normal gland or whether the secretion is so altered in character as to have an entirely different sort of action, and in the dis-

10. Beebe, S. P.: Tr. Assn. Am. Phys., 1906, p. 548.

11. Perry: Some Studies of the Blood in Thyroid Feeding in Insanity, Med. Rec., August, 1906.

12. Beebe, S. P.: Physiology of the Thyroid Gland in Its Relation to Exophthalmic Goiter, Jour. Am. Med. Assn., Oct. 5, 1907, xlix, 1155.

eased condition we must consider the possibility of a defective functioning of other organs which normally are stimulated by the secretion. We have very few methods of estimating the physiologic value of the secretion under normal conditions, the measurement of the protective power to acetonitril poisoning proposed by Reid Hunt[13] being the only one having quantitative possibilities.[14] Until the normal physiology of the gland is better understood we can only deal with the surface indications; and these point to the thyroid gland as one important source of the symptoms in typical cases of hyperthyroidism.

Graves' disease presents a great variety of clinical pictures which in many instances vary so widely from the typical text-book description as to be scarcely recognizable. It has been observed for many years that there is often a progression from a typical Graves' disease through a mixed, indefinite type to a characteristic condition of myxedema. These clinical conditions are the accompaniment of changes in the pathologic structure of the thyroid gland.

Ewing[15] has described four distinct types or stages in the natural history of the thyroid gland of Graves' disease:

1. In the early stages of the disorder, only hyperemia with increase of colloid showing diminished staining reaction with eosin. Microscopically the gland may show no gross changes.

2. Hyperemia with increased colloid, and cellular hyperplasia.

3. Extensive cellular hyperplasia, with increase of imperfect alveoli lined by large or giant cells, and nearly complete loss of colloid.

4. Late stages with fibrosis, atrophy of cells, sclerosis of vessels, hemorrhages and cysts.

There is thus a complete series of changes from the thyroid of early Graves' disease to the pronounced alterations of myxedema, with many intermediate forms, especially in the older cases. It is obvious that the symptoms accompanying changes of such diversity must vary extremely and it is not to be expected that any one treatment, however effective it may be in one stage, can be equally applicable to all stages or types of the disease. Moreover, as the disease progresses, complications may arise in other organs, as, for example, chronic myocarditis, so that the therapeutic problem in advanced cases becomes extremely complex. We

13. Hunt, Reid: Influence of Thyroid Feeding on Poisoning by Acetonitril, Jour. Biol. Chem., 1905, i, p. 33.

14. We have made a series of experiments on this point which will be reported later in detail, but our conclusion is that the method is not suitable for detecting small quantitative differences.

15. Ewing: Pathology of Exophthalmic Goiter in Its Relation to the Serum Treatment, New York Med. Jour., 1906, p. 1061.

do not know how important the relations of the thyroid to other ductless glands may be. The thymus gland has been found hypertrophied in those cases in which autopsies have been made in New York during the last few years, and the lymphatic tissue in general increased in amount. Hansemann[16] is of the opinion that these changes are secondary to the functional overactivity of the thyroid. These facts must be correlated with the high lymphocytosis characteristic of all severe cases and with the fact that it is possible to produce a lymphocytosis by the administration of thyroid to normal animals. It appears, then, that in the young subjects with characteristic symptoms of a recently developed condition of hyperthyroidism we are dealing with a comparatively specific disease which may be alleviated by neutralizing the toxic secretion of the gland; but in the older cases which have existed so long as to cause secondary changes and which may have symptoms of both Graves' disease and myxedema, or which indeed may be a myxedema in nearly every particular, masquerading under the name of Graves' disease because of the primary condition of the patient, it is not to be expected that the serum will have curative effect. And such a conclusion must apply with equal force to the operative removal of the gland or to any form of treatment aimed directly at the thyroid. Analogously, if diphtheria were a chronic disease extending over some months, one would not expect to restore the damaged heart, kidney and nervous system in an advanced case by any amount of serum prepared against the Klebs-Loeffler bacillus and its toxins. There is an abundance of clinical evidence demonstrating the specific action of thyroid preparations in myxedema, and in a small percentage of cases of Graves' disease improvement is obtained by careful thyroid treatment, but by far the majority of typical cases of this disease are made worse by such medication. It is therefore of prime importance to recognize the type of the particular case in order to treat it intelligently. We emphasize this point, because in some instances cases of myxedematous type have been treated by serum, and occasionally, indeed, by operation with very unsatisfactory results.

CLASSIFICATION.

It is impossible to make a comprehensive classification of patients suffering from thyroid disease unless one makes almost as many groups as there are patients. In determining whether a given case is a favorable one for serum treatment it is necessary to study the condition carefully to determine if possible whether the symptoms are those of hyperthyroidism or hypothyroidism. A careful study of the blood, including

16. Hansemann: Berl. klin. Wchnschr., Oct. 30, 1905.

the number of erythrocytes, the percentage of hemoglobin, and a differential leucocyte count, together with a quantitative analysis of the nitrogenous constituents of the urine, will be of value in this respect. In the majority of cases it is possible to decide this point, but we have not found any criterion accurate in all cases and we suggest the necessity for thorough study of the doubtful types in order to establish a more reliable means of classification. The following classification is made solely for the purpose of serum treatment, with a full recognition of the fact that it does not cover all cases, and with the reservation that it is necessary to experiment carefully with many of the atypical cases before one can determine what form of treatment is most suitable. In making these groups we take into consideration the age of the patient, the probable condition of the thyroid, the clinical type of the disease as regards symptoms referable to the thyroid, and also as regards secondary changes in other organs.

TYPES FAVORABLE FOR SERUM TREATMENT.

1. Typical exophthalmic goiter in the early stages, including the incipient, the mild, the severe, and those extremely severe forms which develop very rapidly and have been described as the acute toxemic type, resembling malignant endocarditis.

2. Typical exophthalmic goiter in cases which may have existed for some time in subacute form with occasional exacerbations, but without marked secondary changes.

TYPES THAT MAY REQUIRE COMBINED TREATMENT.

1. Patients who develop thyroidism after reaching the age of 40 or 50 years:

a. Those who, after middle life, show thyroidism for a varying period before the appearance of a goiter.

b. Those who have borne an innocuous goiter for years and late in life develop signs of thyroidism.

2. Atypical forms of thyroidism:

a. Men and more often women of any age who present many signs of thyroidism, but who often have a dry skin and bradycardia and are usually considered neurotic or neurasthenic.

b. Patients with nervous and vasomotor signs of thyroidism, but who complain of a more or less constant headache accompanied in most cases by nausea and abdominal discomfort.

c. The psychopathic cases, the mental disturbance having no definite relation to the severity or type of thyroidism.

The purpose of the classification given above is to serve as an aid in the serum treatment, and in our opinion the groups outlined can not be omitted. Before entering a discussion of the prognosis, the results which we have obtained, and the method of treatment in each separate group, it is necessary to consider briefly some of the simpler fundamentals of the thyroid chemistry.

PHYSIOLOGIC CHEMISTRY OF THYROID PROTEIDS.

There is as yet no agreement among investigators as to the chemistry of the thyroid secretion, and its physiology is even more obscure. Various chemical substances have been isolated from the gland by different methods and it is impossible to reconcile all the statements that are found in the literature. The physiologic activity of the secretion is probably due to the iodin compound which it contains, and we have abundant evidence in the analyses reported by Oswald[17] that the iodin may vary within wide limits, even in health. There has been no demonstration that an iodin-free proteid from the thyroid has any marked physiologic effect. We may believe that the activity of the secretion stands in close relation to its iodin content. It is not known, however, whether the iodin must be in proteid combination to exert its full physiologic action or whether some cleavage product is equally active. The accepted methods of measuring the physiologic value of thyroid preparations do not permit of accurate quantitative distinctions. As a physiologic process the secretion enters the blood or lymph without the intervention of digestion and it seemed to us that its hypodermatic administration would give the best therapeutic results. Saline and glycerin extracts of the gland have, therefore, been preferred and also certain pure proteids have been isolated and kept in solution for hypodermatic administration. The methods followed in making these extracts and proteids were the simplest possible. In the beginning of the work glycerin extracts were preferred, but these caused so marked a local reaction when given hypodermatically that their use was abandoned and a saline extract substituted. This latter solution has been made by thoroughly pulverizing fresh thyroid glands and extracting the hashed mass for from three to five days in five volumes of physiologic salt solution with the addition of a little chloroform to prevent bacterial growth. The extract is filtered first through paper and finally through a Berkefeld candle and sealed in small glass tubes until wanted for administration.

17. Oswald: Ztschr. f. Physiol. Chem., xxxii, 1901, p. 121.

It is not known whether there is more than one iodized proteid in the gland. If one prepares a saline extract of perfectly fresh thyroid glands one finds that a considerable proportion of the proteid therein contained may be precipitated by the addition of acetic acid. From the filtrate a further portion of proteid is precipitated by half saturating with ammonium sulphate. Both these proteids contain iodin and are physiologically active. Oswald[18] maintains that they are identical proteids, and there is certainly much evidence to favor his belief in the case of normal glands. With pathologic glands in the stage of cellular hyperplasia the acetic acid precipitate contains more phosphorus and less iodin than the ammonium sulphate precipitate. With normal glands the amount of the proteid which is precipitated by the acetic acid depends on the freshness of the glands, the concentration of the saline extract made from them and the amount of acid used in the precipitation. Dilute extracts of perfectly normal glands may give no precipitate at all with acetic acid, while a concentrated extract from the same gland yields an abundant precipitate on the addition of acetic acid. Proteids obtained by both methods of precipitation, that is, by acetic acid and by ammonium sulphate, have been administered, but we were dealing with normal glands and it probably made no difference whether we used one or the other, for the evidence indicates that the two precipitates are of the same identical proteid. With pathologic glands, there may be a considerable difference in the therapeutic effect of the two sorts of proteids. The normal thyroid gland differs sharply from other normal glands, such as the liver or kidney, in having a large proteid content which forms no part of a living cell, so that the cell nuclei furnish only a relatively small amount of the proteid in a saline extract. With some of the pathologic glands nuclei are as abundant as they are in liver or kidney and the acetic acid precipitate contains more phosphorus than is obtained from normal gland extract, while the iodin containing globulin precipitated by half saturating with ammonium sulphate is relatively scanty. It is to be expected that proteids having such chemical differences would show differences in therapeutic action. The dose of these pure proteids is very small. We rarely use more than 15 minims of a 1 to 1,000 solution at a single dose, an amount corresponding to the dose of adrenalin. We have been able to get satisfactory therapeutic results with less disturbance of the heart and nervous system by the use of the proteids isolated in this fashion than we have by the use of the commercial

18. Oswald: Die Eiweisskörper der Schilddrüse, Ztschr. f. Physiol. Chem., 1899, xxvii, p. 147.

tablets. The matters relating to the preparation and physiologic value of these proteids are now under investigation and it is quite probable that new methods may be substituted for the ones we have already employed.

These proteids were prepared in the first place in order to alleviate the occasional severe and unpleasant reactions following the use of the antiserum. These reactions occurred more often in those patients who had had the disease for a long time or who had acquired it after middle life. In these two groups atypical cases were occasionally found with some of the symptoms of myxedema, and since the antiserum was not well borne, and because of the many reports in the literature of the successful treatment of such cases by thyroid preparations, we were led to believe that a prothyroid treatment rather than antithyroid treatment was indicated. The hypodermatic administration of thyroid proteids approaches more nearly to physiologic conditions than administration by mouth. Certainly we get more prompt effects by this method and our experience in a large number of cases justifies our belief that pure proteids are more suitable for therapeutic uses than the whole gland substance.

TREATMENT.

In the discussion of the treatment the classification given above will be followed, and the methods and results given under each group. The statistics given in this paper[19] do not include the 105 cases which Dr. Rogers has treated personally, as they are reported in detail at the end of the paper. All of the 141 patients reported herewith, except three which died, have not taken serum for six months and many of them have completed treatment for eighteen months. Serum has been furnished to 126 cases in addition to those which Dr. Rogers has treated, but they are not included in this report for the reasons that some of them are still under treatment and the outcome is undecided, others have not finished treatment for a period of six months, and from a third group satisfactory reports have not been obtained.

Types Favorable for Serum Treatment.—Group 1.—Typical exophthalmic goiter in early stages, including the incipient, the mild, the severe, and those extremely severe forms which develop very rapidly and have been described as the acute toxemic type resembling malignant endocarditis.

19. The statistics quoted in the first portion of the article are taken from the records of one of us (S. P. B.) and are from cases which have been for the most part treated under direction by physicians whose private cases they were. The statistics of the cases treated personally by Dr. Rogers are given at the end of the section on treatment.

It is in this group that we have had the largest percentage of complete success, the most prompt, and the most striking results. This is, perhaps, because in these early cases one is dealing with uncomplicated conditions which favor a specific treatment. It is interesting to note that those who favor operative treatment urge the desirability and even necessity of early surgical removal of the gland if the best results are to be obtained. The incipient and mild cases in young people generally yield promptly to serum treatment. It is probable that a large percentage of these two groups would improve by rest and careful hygienic treatment, and the administration of serum should not be a reason for neglecting these factors; but our experience has shown that serum can arrest these cases promptly. In some cases the entire clinical condition has been changed in a week's time and the symptoms of the disease were no longer discoverable. Patients having mild symptoms do not all recover under rest treatment, and the serum has been used in many of these cases with complete success, after the failure of other forms of therapy.

The simple soft goiters which often develop in young women from various causes are at times accompanied by mild symptoms of Graves' disease. Iodin in some form has been for many years the usual drug treatment of these cases, and in a considerable percentage with the happiest results, but some of them, which in the early stages may not be distinguishable from an incipient Graves' disease, are made worse by such treatment and may develop a typical condition of hyperthyroidism. The administration of thyroid to such patients is occasionally of benefit, but whether given as a means of therapy or for the purpose of establishing a diagnosis, thyroid should be given in very small doses and the effect on the patient carefully observed. This matter will be referred to at a later point in the paper. For these two groups, the incipient and the mild, the serum need not be highly active and may be given at intervals of three to five days. In most of these cases a prompt result may be expected.

We have included in this subdivision the very severe, rapidly developing cases which have many of the characters of an acute infection. This type forms only a small percentage of the total number of cases treated, and yet it is in many respects the most interesting. The very marked improvement caused by the administration of a small amount of serum is quite comparable to the effects seen in diphtheria following the administration of antitoxin. In no other group of cases is the toxemic character of the disease so well shown, and it is precisely with these cases that we have had the most convincing clinical evidence of the antitoxic action of the serum.

The recently developed severe cases take the serum with less reaction than the milder cases, and they may in the beginning take more of it. In some instances we have given a small dose every twenty-four hours until four injections have been given and then have increased the interval to two days. It is necessary to watch the patient carefully for unfavorable reactions, and the serum must not be forced in the presence of marked local and general reaction. The rapid development and great severity of these cases is a bar to surgical removal; the failure of general measures is in sharp contrast to the success of the serum treatment and is, in our opinion, one of the best arguments that can be advanced regarding the nature of the disease and the mechanism by which the serum causes improvement.

The majority of the patients in the first group progress very favorably and many of them recover entirely, which means that all symptoms disappear, under doses of about 0.5 c.c. of an active antiserum given at first as often as the reaction permits and then gradually increasing the interval between injections up to five or seven days. In some cases, however, a small dose of antiserum, 3 to 5 minims, not enough to produce any reaction, given once every twenty-four hours for two or three weeks, will sometimes act better. The best of hygienic surroundings are necessary throughout the treatment, and these, it should be said, are not possible in a public hospital ward, with its attending excitement and often distressing circumstances. In some cases a long time is required to effect a cure or even much improvement, and this means an average of two or three months of antiserum treatment and six months more of restful vacation under constant observation.

Exophthalmos and goiter are the last symptoms to disappear, and as long as the latter persists there is some danger of the recrudescence of symptoms under mental or physical strain. The longer a patient remains free from thyroidism, even with a persistent goiter, the less likelihood there seems to be of the recurrence of the disorder. Some kind of infection, generally tonsillitis, is one of the troublesome causes of accidents and exacerbations. While the entire disappearance of the goiter is a result to be earnestly desired, in the majority of cases it can not be obtained quickly by the serum treatment, and as soon as the more distressing symptoms have subsided it is wiser to reduce the serum gradually and depend in part on hygienic and tonic measures. Occasionally, in the latter stages of the recovery, very small doses, 1/50 or less of a grain, of thyroid proteid act beneficially. If commercial thyroid is used, doses of not more than ¼ of a grain should be given and the effect very carefully watched.

In giving the statistics we have divided the cases into three groups, distinguished by cure, improvement and failure. In order to give an intelligent idea of the results it is necessary to define these terms, and this is particularly necessary because reports in the literature show widely varying conceptions of the term "cure" as applied to the treatment of this disease. By a "cured" patient we mean one in whom the subjective symptoms have been entirely relieved and the objective symptoms have subsided to such an extent that nothing more than a gland discoverable only by deep palpation remains. The majority of the improved patients still have a small goiter, but with most of them the subjective symptoms have been relieved, and the patient has been made comfortable and able to work and act in nearly all respects like a normal human being. It is worth noting that with some of the improvel cases the improvement continues slowly, although the treatment may have stopped for a year or more. The failures are those cases in which the treatment has produced no beneficial effect.

Of the total of 141 cases reported, 52 belong to the first group of the classification. Of these, 18 have been cured, 28 improved (all but 2 being very much improved) and 6 have failed to improve. Of the 6 failures, 3 cases resulted fatally. It should be stated here also that 6 patients properly belonging in this group have applied for serum, which was forwarded as promptly as possible, but in the interval the case terminated fatally before the serum could be given. Such sudden terminations are likely to happen, especially in the very acute form of the disease. Of the three fatal cases listed with the failures, two received only two injections of serum and the third received only one injection. They were of the same acute type as the six cases which terminated fatally before the serum was received. It is impossible to include in a paper of this sort a case history for each patient treated, but the details of a typical cured, an improved and a fatal case are appended herewith.

CASE 1: CURE.—*Patient.*—S. H. C., woman, 39 years old, always well except for attack of grip nine weeks before the development of thyroid symptoms

Signs and Symptoms.—This was a typical acute case, with marked tachycardia; the patient was very nervous, had marked tremor and diarrhea, perspired freely, had troublesome thirst and did not sleep well. Her skin was markedly pigmented; she had marked exophthalmos and a small soft goiter gradually increasing in size. The symptoms of the disease were on the increase; the patient has emaciated somewhat but she is able to be up.

Treatment.—The patient was seen by two prominent clinicians who pronounced it a typical acute case and advised serum treatment. Previous to these consultations she had been treated with rest and tincture of belladonna without beneficial effect.

Result.—The patient was under serum treatment from March 20 to August 31 and continued to improve steadily. The final report received in December states that the very best results were obtained. The gland was normal in size,

tachycardia entirely absent, the exophthalmos cured and the patient stouter than she ever was before and feeling perfectly well. Her color was good, and the appetite and digestion as good as they ever were in her life.

CASE 2: IMPROVEMENT.—*Patient.*—R. M. V., woman, aged 36, married, weight 163, had pneumonia at 17, otherwise healthy.

Signs and Symptoms.—Symptoms first noticed about a year before the treatment began and the patient had lost 94 pounds in weight during this time. The pulse was 108 when the patient was in bed and quiet, of fair quality and regular. The heart was dilated, the apex-beat being one and one-half inches to the left of the mid-clavicular line, faint systolic blow at the apex. The patient was very nervous with marked tremor; perspired freely. She had fair appetite with no vomiting or diarrhea at the time treatment was begun. She was always thirsty. The circumference of the neck at greatest point was 15 inches; a soft goiter of moderate size.

Treatment.—Before serum treatment the patient had been receiving iron, tonics, digitalis and Merck's antithyroidin, but the condition had been stationary for some months. The patient was confined to bed. Treatment was begun in April and continued until September.

Result.—The patient recovered in nearly every particular. There was no noticeable exophthalmos; the goiter could scarcely be seen, but could be felt by careful palpation. The nervousness and tremor were entirely gone. The patient now did her own work and her pulse ran from 84 to 90 after a day's work. There was no systolic murmur and the heart was not dilated. The patient feels perfectly well.

CASE 3: FAILURE.—*Patient.*—I. W. K., woman, 27 years old.

Signs and Symptoms.—This was a typical case with rather slow onset, pulse ranging from 180 to 200, heart symptoms very marked, precordial pain, loud systolic blow, heart dilated, apex beat displaced to the left two and one-half inches. The patient had a hacking cough; her voice was somewhat husky, moderately nervous, with a fine tremor. She slept badly, perspired profusely and had a troublesome thirst. The exophthalmos was moderate; the gland varied in size, at times being small and hard and at others large and soft. There was extreme emaciation, the patient had been in bed three weeks and was very ill when the injections were begun.

Treatment.—This was begun on December 29. Three injections were given by January 4, on which date the patient died.

Result.—There did not seem to be any reaction in either way to the serum.

CASE 4: MARKED IMPROVEMENT WITH SUDDEN DEATH LATER.—This case is very interesting and is included because the manner of death is typical of some of the acute cases.

Patient.—P. J. D., young woman, aged 19, single, history of Graves' disease extending over two and one-half years. The onset of the disease, occasioned by a severe fright, was rapid and progressive.

Signs and Symptoms.—The pulse was 148 and fairly regular; the chest bulged at each pulsation; there was some precordial pain; no heart murmurs; the heart not dilated. Respirations were 27 per minute; there was a slight cough; the voice quite clear. The patient had until recently perspired profusely; her appetite was fairly good and there was no diarrhea. Menstruation had been interrupted for nine months. The patient had become reduced from 145 pounds to 75 pounds in weight. She sat up, but the condition had remained stationary for some weeks. The patient was very nervous with marked tremor.

Treatment.—Up to a month previous to the beginning of the serum treatment the patient had been given thyroid extract. Treatment by serum was given from

November until the following June. The patient began to improve immediately after beginning serum and continued to an almost complete recovery.

Result.—The following report of the patient's condition on September 13 was made: The patient weighs 144 pounds, is able to walk several miles without fatigue, has been doing all the housework for several weeks past. Exophthalmos is noticeable but not marked. Heart is regular, 94, no murmur. The patient is not nervous and has no tremor; sleeps well; bowels and menstruation regular.

Outcome of Case.—The patient died suddenly on October 28 after having had a severe pain in the head for a few hours. There was no autopsy.

Types Favorable for Serum Treatment—Group 2.—Typical exophthalmic goiter in cases which have existed for some time in subacute form with occasional exacerbations but without marked secondary changes.

These cases are, as a rule, amenable to serum treatment, but there is generally not such rapid improvement, and the injections must be continued over a longer period than with the acute forms. In some instances in which the serum has been begun during the period of exacerbation there has been almost immediate relief, in this respect resembling the acute conditions, but permanent results were obtained only after some months. The longer the duration of these cases the slower the patients are to show permanent improvement, but, since we have had complete success with some cases of ten to twelve years' duration, we are led to the conclusion that it is the point to which the disease has progressed rather than the number of years of its course which is the determining factor. If treatment is begun during an exacerbation it should be carried out in much the same manner as with the preceding group, that is, the early acute cases, but it will probably be necessary to continue administration of a weak serum at intervals of five days to two weeks for some months before normal, stable equilibrium is attained.

Of the total of 141 cases reported, 70 have been in this group. Of this number, 16 have been cured, 36 have been greatly improved, and there have been 18 failures, 5 of the latter being fatal. Six patients properly belonging in this group have had a preliminary course of serum treatment and have later been operated on. Three persisted in the serum treatment for a sufficient time to give it a fair trial, with the result that one of them was much benefited and later was entirely cured by operation, while with the two others no decided benefit was obtained and operation, undertaken later, was fatal. The 3 remaining in this group of 6 did not persist long enough in the use of serum to permit any conclusion as to its value, and the subsequent operation proved fatal in each case. The three cases first mentioned as having had serum for some time are included in the list of 141 cases, one as improved and two

of them as failures. The outcome of the operation in the 5 fatal cases can not be ascribed to the preliminary use of serum. Case histories of typical cases occurring in this group are given below.

CASE 5: CURE.—*Patient.*—Mrs. B., aged 44, marked case with history of six years of chronic thyroidism.

Signs and Symptoms.—Pulse 148, irregular; heart dilated, apex 5½ inches from midsternal line; patient very nervous, marked tremor; slept very badly; troublesome thirst; skin pigmented; moderate exophthalmos; irregular menses. Patient emaciated; weight 106 pounds; gland small but firm. Patient confined to bed.

Result of Treatment.—Treatment was given from February to September. In November her physician reported that he considered the patient cured. Her pulse averaged 74; the thyroid could be felt on deep palpation; the patient was not nervous and had no tremors. Exophthalmos could not be detected. The patient weighed 132 pounds, felt in fine spirits, was doing her own work and as far as could be detected was perfectly well.

CASE 6: CURE.—*Patient.*—Mrs. H., 54 years old, member of a highly nervous family.

Signs and Symptoms.—The patient was very excitable and nervous, melancholic at times; had attacks of cardiac dilatation and it was necessary to use morphin to relieve pain about the heart. There was very marked exophthalmos, progressive enlargement of the thyroid, very marked tremor, temperature from 99 to 100, great prostration, and pulse 110 to 140 per minute. The patient's condition was grave for several months. She was under medical treatment for three months and at times showed some symptomatic improvement, but nothing permanent.

Result.—The patient was under treatment for six months. At first she made slow but certain improvement, which has continued progressively, and at the time of the report, two years after beginning the treatment, the patient was well. There was no exophthalmos and no tremor; the patient was not nervous; the pulse was 84, regular, and of good quality; the thyroid could barely be made out, and there had been a great gain in weight, the patient now weighing 175 pounds. The physician considered her completely cured.

CASE 7: IMPROVEMENT.—*Patient.*—Mrs. C. F., aged 46.

Signs and Symptoms.—The patient was extremely nervous; had very marked tremor; slept wretchedly; had troublesome thirst and diarrhea at times. The pulse was 120 to 160; there was pronounced exophthalmos; the gland was only slightly enlarged. The patient had lost 59 pounds, was just able to be up a short time during the day and had lost control of the rectum. She had been very nervous for 12 years, and the physician spoke of her as hopeless.

Result.—Treatment was given from May until October. A great improvement was effected. The pulse was from 80 to 90; the tremor was almost completely gone. The patient made a gain of 30 pounds in weight during this time, was not nervous and slept well. The rectum was under perfect control. The patient was doing light housework and complained of nothing but occasional palpitation on climbing the stairs, but there were weeks when this was not noticed. There was distress at times from flatus in the stomach. Exophthalmos was still noticeable, but not nearly so marked. The size of the gland was about the same. A later report states that the improvement has continued.

CASE 8: IMPROVEMENT.—*Patient.*—Mrs. I., aged 38, had goiter for twelve years, gradually increasing in size. During the last three years the symptoms had gradually been growing worse.

Signs and Symptoms.—The goiter was large, firm, low down on the right side; there was little exophthalmos, marked tremor, pulse when quiet 110, no heart murmur and marked dyspnea on exertion. The patient was very nervous, perspired very freely, did not sleep well and had a variable appetite with occasional diarrhea.

Results.—The patient was under treatment from February to August. There was not much diminution in the size of the gland. The dyspnea was entirely relieved so that the patient was able to do her own work and go out walking for a long distance, which she had been unable to do for years. The heart came down to 80, nervousness and perspiration were entirely relieved, and the patient improved so much that she discontinued treatment.

CASE 9: FAILURE.—*Patient.*—Mrs. M., aged 54; first symptom noticed in 1896. The patient suffered from nervous strain and worry immediately preceding the acute attack.

Signs and Symptoms.—The pulse was 108; there was precordial pain and systolic murmur over the base of the heart. The patient was not nervous and had no tremor; slept fairly well and had a fair appetite. She had a small soft goiter and slight exophthalmos; had lost considerable weight. The most troublesome symptoms were vomiting and diarrhea, also edema of the face and hands. (Diagnosis was questionable.)

Results.—The patient was under treatment from May to October. The serum relieved the gastrointestinal symptoms very decidedly, and the patient was for a time very much improved.

Outcome of Case.—The heart did not improve much, however, and later it steadily grew worse and the patient died in a fatal attack of syncope.

Types That May Require Combined Treatment.—By the combined treatment we mean the administration of both the antiserum and a pure thyroid proteid. The administration of these substances need not be simultaneous, since at one period, generally the beginning of the treatment, the use of antiserum gives the best results, and at a later period the additional administration of a small amount of thyroid proteid is necessary to continue the improvement. If the case presents fairly typical symptoms of Graves' disease, we begin by giving small doses of serum, and in many cases find this treatment followed by very satisfactory relief, but if the serum causes very severe or disagreeable reactions and if there is no corresponding improvement in symptoms we begin the addition of small amounts of thyroid proteid.

In a considerable number of these cases it has been our experience that the administration daily of a small amount of thyroid proteid, three doses of 1/50 of a grain, and the injection of a small amount of serum, 5 minims, every fifth day gives the best results. It is not easy to understand precisely why this is true, since it is paradoxical to believe that a hypothyroid condition exists in the same patient that has symptoms of hyperthyroidism. It may be that the thyroid proteid from a normal healthy animal answers the physiologic need of the patient for such a secretion, while the abnormal product from the patient's own

gland is neutralizel by the use of serum. It is certain that the serum does not neutralize the physiologic action of a sheep thyroid proteid; so that in effect we may, by giving serum and the proteid from normal sheep thyroid simultaneously, substitute the action of the normal secretion from the animal for that of the abnormal secretion from the patient's gland. Whatever may be the explanation, the clinical fact remains that some of these mixed cases improve more rapidly and surely by such a method of mixed treatment.

It is impossible to formulate precise rules to be followed in administering serum to this group of patients, for the reason that the type and clinical conditions are so variable, but from a study of the case we may be able to decide whether the symptoms are a manifestation of hypothyroidism or hyperthyroidism, and the beginning of the treatment should be made in accordance with these conclusions. In my opinion, the logical treatment for the group of mixed cases is the combined treatment, as it combats the dysthyroidism, which is probably an essential factor in the production of the symptom-complex. The treatment of the atypical and the advanced typical cases requires a finer discrimination and more accurate judgment in the employment of antiserum and thyroid preparations than is needed in the treatment of typical cases which form our first group, and it must be admitted that some degree of experimentation must be made with some of these patients before the most suitable treatment is determined on. Complete recovery is slow, but encouraging improvement is often noted in a comparatively short time.

Before we can give treatment intelligently in cases belonging to this group a very careful study must be made of the past history of the disease, the symptoms and the clinical condition in order to determine, if possible, whether the hypothyroid or the hyperthyroid effects predominate, for our therapeutic efforts will be regulated accordingly. The manifestations of these two conditions are so complex and our means of diagnosis so incomplete that we can not always decide in which group a given patient belongs. In most instances it is possible to classify the case, but occasionally we find one of a mixed type that is very difficult to explain.

It will be noted that we have included under the group that may need combined treatment the atypical cases and cases of those patients who develop thyroidism comparatively late in life. The patients in atypical cases are not necessarily advanced in years, many of them being under 30, and the typical patients over 50 do not all need combined treatment, so that the factor of age can not be the criterion by which the matter is decidel.

The cases belonging in the atypical group are much the most difficult to classify and treat. None of them have all the typical symptoms of Graves' disease, and the majority of them appear to suffer from an abnormal secretion rather than a pure hyperthyroidism. They have often come to us with the diagnosis of Graves' disease because they have at one time had a typical form of the disease, but as we see them they have passed out of that typical form to the mixed type and occasionally one appears to have a nearly complete myxedema. Such cases are not to be treated by serum alone. Surgery is equally out of the question or should be with most of them.

In order to bring the matter more directly in view we append a table of contrasts to show the differing symptoms of hypothyroidism and hyperthyroidism. For the hyperthyroidism typical Graves' disease is the best example, but for the opposite type we have selected the myxedematoid rather than typical myxedema in advanced stages.

HYPERTHYROIDISM.	HYPOTHYROIDISM.
AGE.	
More common in young women, 18-30.	More common in advancing years, 35-50.
ONSET.	
May be slow and gradual or sudden and acute.	Slow and gradual, in many cases engrafted on an old Graves' disease.
HEART.	
Tachycardia 120-180; pounding beat felt over wide area; often a loud systolic murmur over apex, base and along the great vessels. Irregular and very susceptible to the effects of exercise. Blood pressure variable, generally low, pulse soft and full, marked dyspnea on slight exertion. Marked edema of legs.	Rarely above 100, may be irregular with heaving impulse. Pulse generally shows high tension and the blood pressure is above normal.
NERVOUS SYSTEM.	
Fine tremor affecting nearly all the muscles, twitching, and occasionally spasms. Patients are abnormally irritable and excitable, apprehensive, mentally *very* active and physically restless. Muscular weakness prominent.	Patient may have some tremor, and muscular weakness is likely to be very pronounced, but there is not the same restlessness and jactitation. Patients are occasionally irritable, but they are generally rather dull and apathetic, mentally slow; memory defective. Pains in joints frequent, and there is a marked tendency toward sudden giving-way of the legs when walking.
EYE SIGNS.	
Exophthalmos generally present, although it is not invariable. Occasionally unilateral, corresponding to the side having the enlarged thyroid lobe. Various symptoms arise in consequence of the exophthalmos. No pupillary changes.	Exophthalmos is unusual, although it may have been present at one time.

GLAND.	
Enlargement varies from nothing to very large goiter. The blood vessels over the gland are generally much enlarged and pulsate markedly. Right lobe generally the larger.	Often no enlargement can be made out; when there is a goiter it has an elastic, rubber-like consistence, occasionally cystic and nodular, but very distinctly different from the active, pulsating gland of Graves' disease.
NUTRITION.	
Severely disturbed; in most cases there is a loss in weight, which may progress to extreme emaciation. Appetite variable; vomiting and diarrhea frequent complications. Patients drink a great deal of water.	Generally not seriously disturbed; patients hold their weight and in most cases gain slowly; constipation rather than diarrhea, and flatulency a troublesome habit. Patients do not drink much water.
SKIN.	
Profuse perspiration, erythema, urticaria, dermographia; pigmentation, which may occasionally be so marked as to suggest Addison's disease. Hair falls out, but is not coarse and dry. Patients prefer thin clothing and cold rooms. They are more comfortable during cold weather than during hot weather.	Dry, may be scaly; patients do not perspire on exertion; hair dry, brittle, scalp scaly. Pigmentation not common. Patients prefer thick, warm clothing and are cold most of the time. Much more comfortable during hot weather.
TEMPERATURE.	
May be only slightly elevated, 99-100. With severe acute cases it runs often to 102-104.	Subnormal, may reach as low as 95.
URINARY FINDINGS.	
In most cases normal in volume; glycosuria not unusual; polyuria often observed in later stages. Nitrogen partitions show a very much decreased kreatinin excretion, while kreatin is present in large amounts. Nitrogen loss is marked during the period of emaciation.	Albuminuria not unusual. Nitrogen partitions do not show so marked a disturbance in kreatinin and kreatin ratios. In large number of cases urine practically normal.
BLOOD.	
Hemoglobin low, leucopenia in severe cases, with a marked relative lymphocytosis.	Hemoglobin low, white blood count normal.
MENSES.	
Very irregular or completely suppressed.	Generally regular but scanty.

The atypical cases do not fall sharply into one or the other of these groups, but show most unusual combinations of symptoms of pure Graves' disease with those of myxedema. The existence of such cases has been recognized for some years and their successful treatment with thyroid preparations is not new. It has been our observation, however, that a large percentage of these patients do not do well on thyroid extract alone, and that a combination of serum with thyroid proteid gives the best clinical results.

The statistics which are given under the last two groups do not furnish an accurate estimate of the prognosis in those types because we have used the combined treatment only during the last year and there are comparatively few who have finished the treatment for a period of six months. My list shows 19 cases which fill this requirement, however, and of these 10 have been greatly improved and 9 have failed of improvement. There have been no deaths in this group and no patients have been cured. It is only fair to state that there have been 4 cured patients, but they have not finished treatment for a period of six months as yet and so they have not been included.

CASE 10: IMPROVEMENT.—*Patient.*—Miss H., aged 40, had had subacute symptoms for ten years.

Signs and Symptoms.—The pulse was 120 to 140; respirations about 20 and labored; voice rather husky. The patient was rather nervous; had no tremor; could sleep only in a semirecumbent position; had a good appetite; had diarrhea, pronounced exophthalmos, a small soft goiter, and was slightly emaciated. Her condition was stationary for some time.

Results of Treatment.—The serum was used for six weeks with some general improvement in the condition of the heart, but the gastrointestinal condition was not relieved. During the next six weeks the combined treatment was given with the best results. The pulse dropped to 98, exophthalmos was much less, the diarrhea completely relieved, the thyroid much softer and almost normal in size. The patient slept well in recumbent position; was rapidly improving and felt equal to resuming her occupation as a teacher. A later report states that her satisfactory improvement has continued.

CASE 11: IMPROVEMENT.—*Patient.*—Miss N., aged 38; history of Graves' disease for six years.

Signs and Symptoms.—The pulse was 120 to 130; there was slight precordial pain and tremor, especially pronounced in the hands and knees, and the appetite was poor. The patient was very nervous, slept badly and was troubled with diarrhea and sometimes with vomiting; had marked exophthalmos, a small hard goiter; was emaciated and not able to be up.

Results of Treatment.—Treatment was continued from May until October with the result that the patient gained 30 pounds in weight; pulse became regular at from 80 to 90; the appetite good; no diarrhea; menses regular; nervousness entirely relieved. "In short, her general condition is very good."

CASE 12: FAILURE.—*Patient.*—Mrs. G., aged 56; history of goiter for twenty years with symptoms of an atypical Graves' disease for eight years.

Signs and Symptoms.—Patient was nervous; did not sleep well and had a poor appetite with occasional diarrhea. Pulse was from 90 to 100, regular and of fairly good quality. There was no troublesome perspiration or unusual thirst. The patient had had moderate exophthalmos in the past, but this symptom was no longer seen. Headache was a troublesome feature of the case. Temperature was normal.

Results of Treatment.—The case was not considered a favorable one for treatment with serum, but it was begun cautiously and was carried out for some time with no benefit. Later the combined treatment was tried for a period of six weeks without benefit. Patient was no better in any way than at the beginning of the treatment.

The patients personally treated by Dr. Rogers to Jan. 1, 1908, number 105, who presented, more or less markedly, the three cardinal signs of exophthalmos, goiter and tachycardia. Reports could be submitted on about 100 additional cases, but, as they were mostly hospital or consultation patients whose records are incomplete or people who presented irregular and doubtful forms of thyroidism, it has seemed best to confine the report to those that have been personally treated throughout and to typical examples of exophthalmic goiter. There is thus no question about the diagnosis and it gives a clearer understanding of what has been accomplished for these sufferers.

Of the 105 patients, 12 have been cured of every trace of disease, including both exophthalmos and goiter, 17 have no symptoms of a pathologic nature whatever except a small goiter in a few instances, and one has a slight right-sided exophthalmos but no goiter. As neither of these abnormalities is noticeable without close examination, I (J. R.) think it is fair to group these cases together and state that a total of 30 have been cured.

Forty-three who have undergone specific serum or combined treatment have been improved, and, while some of these are still under treatment, many of them are expected to be ultimately in the cured class.

Four have failed to show any benefit by specific treatment.

Seven whose condition in several instances was at first greatly benefited by the antiserum have died from the natural progress of the disease.

Twenty-one have been operated on either before or after undergoing the specific treatment described below, with the result that none can be called a perfect cure, and two of these 21 have died as a direct result of the operation.

A brief analysis of the failures, the deaths and the operative cases presents much that is instructive. The four described as failures under antiserum received no other treatment and occurred early in our experience before we had grasped the importance of supplementary thyroid treatment at certain stages, or in certain forms of the disease. Nevertheless, in so complicatel and obscure a disease it is only reasonable to expect a considerable percentage of failures for a long time to come, or until there is a much more definite understanding of the physiology of the thyroid than exists at present.

One of the most striking features in a survey of all the 105 cases is the gravity of the prognosis, for, in spite of everything which could be done, there was a death rate in this comparatively brief period of observation of less than three years, of approximately 10 per cent. One

gains the impression from the observation of many patients in different stages of exophthalmic goiter that the mortality under ordinary medical treatment is considerably higher than this. Indeed, the expectation of life after the onset of the symptoms in a well-marked case can not be more than ten or twelve years.

The best results occurred in the very severe acute or the early mild cases, especially if the goiter was small. The failures and deaths occurred in cases of marked severity with large goiters and after the disease had been manifest for several years or in patients who developed it late in life. There have, however, been some exceptions to these rules, as a few with small goiters have done poorly while others which appeared almost hopeless have progressed surprisingly well. Five women while in the improved class have gone through a normal pregnancy with continued gain, and all but one were delivered at full term of healthy children. Antiserum was given in three cases throughout the pregnancy; the other two were so well during this period that no treatment was required.

Two of the five mothers can now be placed in the cured group, though one still has a barely perceptible goiter, but no other symptoms. The surviving children show no abnormality. In reviewing the histories of all the patients, however, the heredity was quite apparent in a considerable number of the cases. It was not unusual to elicit a more or less close family history of goiter and in a few cases of true exophthalmic goiter, but the proportion was not greater than in other diseases like tuberculosis, rheumatism or cancer.

Two patients presenting a well-marked though not particularly severe type of the disorder of several years' duration made an almost complete recovery after a few months of antiserum treatment. The exophthalmos, tachycardia and subjective symptoms entirely disappeared, but the goiter remained quite large, though softer than at the time of the first observation. During this period a considerable degree of rest, quiet and good hygiene had been enforced, but as soon as the patients felt well work was resumed, by one as a book canvasser, by the other as a tailor in a sweat-shop, and very soon thereafter during a time of hot weather and hard work, a combination which seems particularly trying, both patients relapsed. Antiserum seemed to do harm, prothyroid treatment was without avail, and the disease progressed gradually to a fatal termination which was preceded by stupor and coma.

A third patient had almost the same history, but by a careful use of antiserum and combined treatment, apparently with beneficial results, barely escaped death and has now no symptoms except of small goiter.

Of the 21 patients operated on 3 had only the superior thyroid vessels ligated. The 18 remaining patients underwent the more radical and generally recommended operation of removal of a portion of the thyroid gland either before or after submitting to the specific thyroid medication. And these 18 are the most important from a surgical standpoint.

Nine patients had been operated on and had relapsed before coming under observation, and some of them had reached a condition worse than that which had called for the interference. Three of these nine had each undergone two operations with no lasting benefit. Of the nine who relapsed after radical operation, four have been greatly benefited by the antiserum or by prothyroid treatment and might be called cured if sufficient time had elapsed to demonstrate that another relapse will not occur. Three have so much improved as not to be conscious of illness, although some tachycardia is still perceptible. One (who has had two operations) completely failed to improve in spite of careful treatment and is slowly but surely losing ground, and the other, who also had had two operations, failed entirely under the antiserum, and in July, 1907, suffered a removal of the second thyroid lobe, leaving only the isthmus. This, in November, 1907, was evidently enlarging, and, though the patient had after the last operation, as after the previous two, gained considerably in flesh and strength, both subjective and objective symptoms were very apparent, and she stated that she felt little, if any, better.

The remaining nine patients, after failing to improve under the antiserum treatment, suffered removal of one lobe and the isthmus of the thyroid gland either at the hands of Dr. Rogers or at those of other surgeons. Of these, two died of acute thyroidism (?) shortly after the operation. The first came under observation early in my experience with a very severe toxemic form of the disease, and when the antiserum was begun death seemed imminent. After two or three months of antiserum treatment she almost entirely recovered, but still had comparatively mild symptoms and a pulse rate of 110. In an attempt to complete the cure, the right lobe and isthmus were removed with a fatal result. The other death occurred in a psychopathic case with mild symptoms of Graves' disease and melancholic depression, with delusions of sight and hearing. Antithyroid and prothyroid treatment were both tried and seemed only to make the psychosis worse, so removal of one lobe of the much hypertrophied gland was attempted and a fatality followed within two days.

The seven remaining patients were all treated with antiserum with more rather than less unfavorable results, although five were at first greatly improved and then remained stationary or were made worse by the

medication. I believe now, however, that with time and good hygiene and the judicious exhibition of the combined treatment, the advantages of which have only of late become apparent, much more could have been accomplished. Nevertheless seven patients, after failing to recover under antiserum treatment, had one lobe and the isthmus of the gland successfully removed, and the last operation on these cases was in October, 1907. Only three of the seven were much benefited by the operation. One who was operated on in November, 1906, remained comparatively well though unable to undergo vigorous exertion until February, 1908. The second patient, after gaining somewhat under antiserum, relapsed and had the left superior thyroid vessels tied and the right lobe removed in Stockholm in September, 1906. After this she gained slowly in flesh and strength and returned to this country, but suffered another relapse with typical symptoms in November, 1907. The third patient came under observation in July, 1907, and refused operation after appreciable benefit from the antiserum, especially in the very troublesome insomnia and weakness. He then left the hospital and relapsed in December, and in January, 1908, had one lobe and the isthmus removed, and, although much improved, still shows in April the characteristic symptoms.

The other four of the seven patients who underwent operation after failure with the antiserum are about as they were when first seen and at least two of them were for several days after the operation in a rather critical condition and convalesced to their original state very slowly.

These experiences, while not very extensive, have seemed to indicate that when antithyroid, or in very exceptional cases, prothyroid treatment fails, not much can be promised by radical surgery. Not only the danger but the uncertainty of the result of operative removal of part of the thyroid in exophthalmic goiter demands that until there is a more definite knowledge of the physiology and pathology of the organ, at least a trial should be made of the specific treatment.

According to these statistics about 30 per cent. of all cases under careful management can be practically cured and the earlier they come under treatment the better the prognosis. About 50 per cent. can be improved; some 20 per cent. have failed and of these 10 per cent. have already died. This includes all stages and varieties of the disease; the youngest patient was 5 years of age and the oldest over 80; many have been sent for specific treatment as a last resort and have been considered hopeless at the outset, but the inclusion of all patients without distinction so long as the diagnosis is unmistakable, is the only method by which a reasonable idea of the prognosis can be derived.

THE REACTION FOLLOWING THE INJECTION OF SERUM.

The serum is always given by hypodermatic injection, and we have chosen the arm as the site of injection because it is more convenient for the patient and because the local reaction causes less trouble in this region and may be treated more readily. The upper arm just below the deltoid should be carefully cleaned and the injection made subcutaneously but not intramuscularly in order to avoid too rapid absorption. In 95 per cent. of the injections the local reaction consists only of an area of hyperemia and slight induration which may be somewhat tender on pressure for a few hours. It quickly clears up and in thirty-six to forty-eight hours the arm is perfectly normal. The indurated area may in some instances be three or four inches in diameter and occasionally the whole arm has become edematous from the shoulder to the finger-tips. Such a reaction is unpleasant but fortunately it is a rare complication and if the arm is wrapped in a wet dressing the reaction subsides without unpleasant after-effects. The exact nature of the reaction in any given case cannot be foretold because the matter of personal idiosyncrasy of the patient is an exceedingly important factor. It is best, therefore, to start with a small dose and to determine the nature of the reaction in each case before the full therapeutic dose is attempted. As has already been stated, the very acute toxic cases take the serum better than the mild cases and with them it may be best to begin with a full dose. If the local reaction is marked it is best to keep hot applications on the arm for half to three-quarters of an hour after the injection, and gently massage the area about the point of puncture. Unless some quite unusual condition results no further treatment is necessary, for the condition subsides promptly. If a second injection is made before the reaction from the first has subsided a more decided reaction is produced in the second instance and the area of the first injection is again excited. The local reaction is therefore of value as a guide in the determination of dose and frequency of administration. The two arms should be used alternately at the site of injection.

The general reaction likewise shows considerable variation. In a large percentage of cases there is no disturbance whatever; there may be, however, a slight rise in temperature accompanied by nausea, some restlessness and perhaps some increase in the tachycardia. Rarely the patient may vomit and all the symptoms of the disease be temporarily exaggerated. If the serum is given too frequently or in too large doses both the local and the general reactions become more severe. The serum must never be pushed in the presence of a progressively increasing re-

action. Serious consequences may arise if this precaution is not observed. If, during the course of treatment, an usually severe reaction has been obtained it is best to allow a somewhat longer interval before the next injection, and at the same time to reduce the dose.

During the last two years the study of the phenomena of anaphylaxis[19] and of the so-called "serum disease" has directed attention to the complications of serum administration. Several instances of severe reaction, some of them even with fatal outcome,[20] have been published recently and it is evident that serious consequences may occasionally arise. (None of the reactions to which reference is made have occurred in the use of the thyroid serum.) We have tried to avoid such possibilities by giving the serum in the first portion of the treatment at short intervals, that is, from one to five days, and thus avoid sensitizing the patient. In spite of these precautions we have had out of the several thousand injections that have been made in the course of the last three years, a few very severe, and, for the time, alarming reactions, although none have been fatal. These have been obtained in cases which have had the serum for some time and have occurred without any previous warning. (It is only fair to state that nearly all of the reactions occurred in the earlier part of our experience when we were using somewhat larger doses than we now find necessary.) These reactions have developed in most cases very shortly after the injection of the serum, but in a few instances the onset has been delayed for a couple of hours. They have always occurred in patients who have had some previous treatment with the serum. The reaction develops rapidly and resembles in some respects the condition recently described by Ohlmacher[21] as occurring in two cases treated with antistreptococcic serum. The cutaneous surfaces of the face became very much swollen, the nose, lips and ears were of twice the normal size and the exophthalmos was likewise much exaggerated. There has been some subjective distress, particularly in breathing and the patient has become markedly cyanosed with a rapid, feeble pulse and a more or less pronounced syncope. The reaction is alarming for both patient and physician; but in our experi-

19. Rosenau and Anderson: A New Toxic Action of Horse Serum, Jour. Med. Research, 1906, xv.

20. Gillette, H. F.: Diphtheria Antitoxin in Bronchial Asthma, Jour. Am. Med. Assn., 1908. Wiley, S. N.: Sudden Death from Injection of Diphtheria Antitoxin, Jour. Am. Med. Assn., 1908, l, 137. Boone, L. L.: Sudden Death Following Use of Diphtheria Antitoxin, Jour. Am. Med. Assn., 1908, l, 44. Quigley, I. K.: Collapse After Use of Diphtheria Antitoxin, Jour. Am. Med. Assn., 1908, l, 768.

21. Ohlmacher, A. P.: Two Instances of Severe Non-fatal Serum Reaction, Jour. Am. Med. Assn., 1908, l, 875.

ence the condition has rapidly improved and an hour later all evidences of the attack may have passed off. We do not know why such a reaction should develop but it is probably related to the phenomena of anaphylaxis. There is probably some peculiarly susceptible condition of the patient at the particular time the injection is given, for the patient may have taken the same serum previously without any marked reaction, and may continue to take it again for weeks without ever showing again a reaction at all like this. We have learned to combat these severe reactions with the hypodermatic injection of thyroid proteid, but their great infrequency makes it probable that very few physicians will ever have occasion to deal with them. Since we have given the serum in smaller doses at shorter intervals we have seen few disturbances other than the local reaction in the arm. Following such a reaction no serum should be given for a week and then a somewhat smaller dose should be given for the first injection. The serum produced in each animal varies somewhat from that of other animals so that it is necessary to know the character of the serum and the condition of the patient before the question of dosage can be decided.

The relation which the specific treatment bears to the surgical treatment is naturally of much interest. The list of 141 patients includes 8 who have had some surgical procedure for the condition. Six of these cases have already been described. The two others are interesting as they both are instances of recurrence after operation; one of them is of especial interest as it is the first case in this country of a patient undergoing surgical treatment for the relief of Graves' disease. Brief histories of these two cases are given below:

CASE 1.—*Patient.*—Mr. F., aged 28, had the disease for eight years, operated on; had the right lobe, isthmus and part of the left lobe removed, "improving the fast pulse, exophthalmos and nervousness." Still had attacks of diarrhea and tremor; pulse was 109; the patient slept badly; had lost 35 pounds in the last three months and was unable to work.

Results of Treatment.—The patient was under treatment for six weeks. Improvement began with the first injection; the tumor was greatly reduced, diarrhea cured, tremor greatly reduced, he can walk a good distance without undue fatigue. Has gained 27 pounds since the treatment began and is in every way much improved.

CASE 2.—*Patient.*—A woman of 34 years, weight 130, physical condition typical of Graves' disease, tachycardia of 116 to 140, heart otherwise normal, nervous with marked tremor, small goiter of medium consistence, increasing in size during the last few weeks.

History.—This patient was the first to have removal of gland in this country for the relief of Graves' disease. The operation was done by Dr. A. C. Bernays in St. Louis May 13, 1894. The right half of the gland was removed and the superior artery tied on the left side. The condition previous to the operation was serious, but the patient was entirely relieved and remained well during thirteen years

following the operation. There was redevelopment of the disease in the spring of 1907. Her condition has been growing worse. Treatment by rest, ice pack and quinin hydrobromate had not improved the condition.

Results of Treatment.—Ten injections of serum were given; the first caused a marked reaction, the second much less, and it gradually decreased to no reaction whatever, "and with this the pulse kept growing slower, she gained in weight, the goiter grew less, and every symptom gradually disappeared."

To summarize these cases again, it will be recalled that five patients tried serum first without benefit and later died as a result of operation, two were operated on before the serum treatment with good result and were later treated successfully with serum for a recurrence of the disease, and the last was benefited considerably by serum treatment preliminary to a completely successful operation. As far as these figures go it would seem that if a case can not be benefited by serum it may be dangerous to operate; and also that, if an operation is likely to be successful serum may also be successful. It appears to be true that the type of case which can be completely cured by operation is a type favorable for serum treatment.

It must not be understood that what has been said above is a criticism of or an argument against the operative treatment. The few brilliant operators who have had sufficient experience to select the cases intelligently, give the proper preliminary treatment, and carry out the operative procedure with the requisite skill and judgment have had very good results and their statistics speak for themselves; but the fact remains that for the majority of surgeons the operation gives a high mortality and not fully satisfactory postoperative results. Moreover, I think the time has not yet come to determine precisely what the results of operative procedure are to be. Surgical removal of the thyroid for Graves' disease can scarcely be considered an emergency operation, and in my opinion should not be undertaken unless the operator is thoroughly familiar with disease, and has had his judgment tempered by a wide experience.

Graves' disease is a serious malady and should be so regarded. The fact that incipient cases in young women will in most cases improve promptly with rest and tonic treatment is a cogent reason for early recognition of the condition, but even in early cases there are many that do not terminate so happily but continue to progress toward an acute development of hyperthyroidism. Again it is often found that the rest cure is only temporary and that as soon as activity is resumed the serious symptoms again appear. The earlier symptoms may not be such as to disturb the patient and she may be thought merely nervous. In many

of our cases the condition has been first noticed by the patient's friends or by the physician at a time when the patient feels perfectly well. The analogy between Graves' disease and health urged by Putnam[22] is of considerable importance. He says:

> The symptoms of Graves' disease shade off, if one studies a large number of cases, into the phenomena of health. The tremor, the rapid and excitable pulse, the flushed skin, the restlessness of mind, are seen almost habitually in many persons who are simply called nervous, and these symptoms and more, including the staring gaze, may come on suddenly, even in a presumably healthy person, under the influence of a strong emotion, which may be called either a disease or a quasi-physiological state. . . . . I will repeat in conclusion that the importance of the analogy between Graves' disease and health is urged, not as an exclusive theory, but as one profitable mode of regarding the subject.

It is, of course, impossible from the data at our disposal to determine the precise value of the serum in the treatment of hyperthyroidism. I believe that as far as numbers are concerned an equally large series may be shown which have done as well or perhaps better on purely medical treatment, but the type of case counts for everything. Practically all of the first 100 patients and at least 75 per cent. of the remainder have used the serum only as a last resort after having tried rest, tonics, thyroidectin, and a great variety of medical measures without relief. In many such cases when the gamut of general therapy has been run the serum has been given with the most striking and immediate benefit. In the majority of cases, however, the improvement, although positive and undoubted, has been slow and gradual, perhaps requiring six to eighteen months for the final complete recovery. This is not in any way unusual, since recovery after surgical removal of the gland is in many cases slow, requiring one or two years.

CONCLUSIONS.

This work is the first attempt to treat disease in the human subject by means of a specific cytotoxic serum, and our own conclusions, subject to revision as experience increases, are as follows:

1. The serum has a specific effect in neutralizing the toxic action of the thyroid secretion.

2. As a therapeutic agent it gives results which can not, in many cases, be attained by any other medical means.

3. Not all cases presenting symptoms of thyroidism can be treated successfully with serum, because not all cases are purely hypertrophied in origin.

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22. **Putnam**: Clinical Aspects of the Internal Secretion, Tr. Cong. Am. Phys. and Surg., 1897, iv, p. 122.

4. The rapid amelioration of symptoms in the acute toxic cases, similar in most respects to the well accepted instances of neutralization of toxin by antitoxin, is a weighty argument in favor of believing the symptoms to be due to the toxic effects of hyperthyroidism.

5. The beneficial results of combined treatment, especially in the older cases, indicates a *dysthyroidism* as well as *hyperthyroidism* as a factor in the production of symptoms.

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ACIDOSIS AND ASSOCIATED CONDITIONS.*

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GENERAL STATEMENT.

The idea that the body may become poisoned by acid humors dates from the legendary days of medicine, but the conception of an intoxication referable to acid products of metabolism is a result of the rigid application of chemical laws to physiologic processes.

The theory of acid intoxication in its current form attributes to the acid action of principles arising from processes of metabolism a definite symptom-complex, occurring chiefly in diabetes, but seen in less striking form in many other diseases. For carnivorous animals it is easy to name the sources of such acid products of metabolism. They are found in the high phosphorus and sulphur content of the protein molecule, which, on oxidation, yields phosphoric and sulphuric acids. They appear in the long series of fatty acids which form the combustion-products of the fats. They arise also in the series of changes in carbohydrates from glycogen through glucose to lactic acid. From all these foodstuffs, especially the proteins and fats, the main tendency in metabolism is toward the production of acids. The exclusive flesh diet of carnivora increases this tendency; but the mixed diet adopted by man includes one prominent contrary factor in the rich alkalies of vegetable cells; while in herbivora the conditions are least favorable for the accumulation of acids in food metabolism.

The theory of acid intoxication regards only the chemical properties of these acids, and this property is to unite with alkalies. The sources of the alkalies which are available for the neutralization of acids are, first, those of the cells, and second, those of the blood and lymph; and it is the abstraction of the fixed alkalies of the organs and those of the blood which is believed to be responsible for the disorders of function and the symptoms of intoxication. Hence, it is the functions of the alkalies of the body which determine the symptoms of acid poisoning. Here it is obvious that vital processes are involved, for the function of respiration is dependent on the alkalescence of the blood; the solution

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of globulins in protoplasm is maintained by association with chemical bases; and the actions of ferments, digestive, circulating and intracellular, are determined by the reactions of their media. So that the theory of acid poisoning begins with the principles of normal food and tissue metabolism, recognizes in many conditions a mild grade of acid excess, which Naunyn called "acidosis," and finds its clearest expression in the acid intoxication of diabetic coma.

General chemistry, physiologic chemistry and, more recently, physical chemistry have all contributed essentially to our knowledge of acid intoxication, while the interpretation of the phenomena observed forms an important chapter in physiology. The clinical aspects of the subject, also, are among the most complex in general medicine, so that the development of the doctrine has been slow and difficult.

In a review of our knowledge of this topic, which is the object of these lectures, all the above departments require special consideration. It is proposed, therefore, reversing to some extent the order in which the knowledge was acquired, to present, first, the experimental basis of the doctrine of acid intoxication, and to consider the general problems as presented in the most pronounced form of acidosis, that of diabetes; second, to discuss the physiology and physiologic chemistry of the substances concerned; and third, to deal with the various diseases in which acidosis occurs, and determine, as far as may be, the significance of acidosis in such conditions as starvation, acute yellow atrophy, eclampsia, delayed chloroform poisoning, cyclic vomiting of children, gastrointestinal diseases and phosphorus poisoning.

I. EXPERIMENTAL BASIS OF ACID INTOXICATION—DIABETIC ACIDOSIS.

1. Poisoning by Mineral Acids.

The first clue pointing to the occurrence of acid intoxication appeared in the work of Boussingault, who, in 1850, found that diabetic urines usually contain very large amounts of ammonia. To-day these results must stand as indications of excessive excretion of acids, but Boussingault's methods were attacked, and prevailing opinion, as stated by Nasse, and experimental results of Eylandt, Wilde, Gaethgens and others, indicated that administration of acids entailed no great loss of alkali in the urine and no serious disturbance of the alkalinity of the blood.

On the other hand, Miquel, by administering sulphuric acid by mouth in dogs, and Salkowski, by poisoning rabbits with taurin, which yields sulphuric acid in the body, demonstrated extensive loss of alkali in the

urine, while Lassar, by direct titration with acetic acid, found marked loss of alkalescence in the iced blood of various animals poisoned by acid.

The pathologic significance of the withdrawal of alkalies by administration of mineral acids seemed to be placed beyond doubt by the work of Walter, who showed that 0.9 gm. of hydrochloric acid by mouth per diem was constantly fatal for rabbits, and that the carbon dioxid content of the still faintly alkaline blood of such animals was greatly reduced. Organic acids, in his hands, were without comparable effect. Dogs failed to react to hydrochloric acid with toxic symptoms, and Walter's experiments show that this animal possesses an immunity against acid intoxication, protecting its blood alkalies by neutralizing 75 per cent. of the acids with ammonia. Since the symptoms in rabbits at the last stages of poisoning from 2 gm. of acid could be promptly relieved by intravenous injection of 0.5 gm. sodium carbonate, Walter concluded that the symptoms were referable solely to the withdrawal of alkali.

The symptoms of the acid poisoning appeared to be characteristic. The respiration was accelerated and the inspiratory movements were deeper and labored, while the blood pressure rose with tumultuous heart action. Later the dyspnea ceased, respiration failed, the heart became feeble and blood pressure fell. Walter was not impressed by the autopsy findings, except for gastric lesions produced by the acid, which he found difficult to avoid.

The study of the effects of administration of acids in animals has been pursued by many observers during the past thirty years, with the result of greatly extending and, in the main, confirming the conclusions of Walter, and these results have furnished the main experimental basis of the doctrine of acid intoxication. It has further been shown that rabbits may protect themselves to a certain extent by the formation of ammonia (Winterberg) and are less susceptible when on a protein diet. Eppinger was able to delay or prevent the symptoms in rabbits by feeding them on beef blood or egg albumin and by subcutaneous injections of amino-acids; while, after rectal injections of glycocol, he found that rabbits neutralized 75 per cent. of ingested acids by means of ammonia. (The contrary results obtained in this field by Pohl and Münzer have been set aside by Loewy.) On the other hand, starving dogs are just as susceptible to acids as are normal rabbits (Eppinger), and dogs readily succumb to the intravenous infusion of acids (Eppinger, Szili).

Typical acid intoxication in rabbits has been produced by phosphoric acid (Kobert) and by acid sodium phosphate (Spiro), but in dogs the acid effect was obscured by the action of the salt. Eppinger produced the usual symptoms of acid intoxication in rabbits by lactic acid.

All these results go to show that in dogs and rabbits there is a direct relation between the poisonous effects of acids and the acid-neutralizing resources of these animals, and that these resources may be altered almost at will by regulating the supply of alkali. The dog protects itself against acids readily because of its protein food, which furnishes an abundant supply of ammonia that may with safety be diverted from urea formation to neutralize the acids, while the rabbit, ordinarily without such source of ammonia, and compelled to call on the fixed alkalies for the neutralization of acids, may yet be supplied with ammonia by protein food. There appears to be no essential difference in metabolism between the two animals. Yet there is an important difference in the readiness with which these animals utilize proteins in the formation of ammonia, and this difference, Eppinger finds, depends on the size of the pancreas in the two animals. In the rabbit the pancreas is small, and whole proteins or their complex cleavage products, as polypeptids, are slowly broken up in the intestine, whereas glycocoll does not require further digestion, but may be readily absorbed and serve as a source of ammonia. A depancreatized dog Eppinger found to be more susceptible to acid poisoning than the rabbit (Szili). These facts may be of significance in connection with the pancreatic lesion of diabetes. According to this view, a simple quantitative deficiency in the digestive function of the pancreas may reduce the supply of absorbed amino-acids and the ammonia available for the neutralization of fatty acids and thus favor the development of acid coma.

ALKALESCENCE OF THE BLOOD IN ACID POISONING.

The explanation of the toxic effects of the withdrawal of alkalies from the blood and tissues is suggested by the diminished alkalescence of the blood and its lowered content in carbon dioxid. In fatal acid intoxication the blood may contain only 2 or 3 volumes per cent. of carbon dioxid as compared with the normal 28 to 40 per cent. (Walter), and Spiro found only 1.6 volumes per cent. in the blood of a dog receiving acid sodium phosphate. By direct titration Spiro observed in dogs a fall in blood alkalinity from 169 to 73 mg. sodium hydrate per 10 c.c. of blood. Szili infused 1/8N hydrochloric acid into the jugular veins of rabbits and dogs, 2 c.c. per minute. The rabbits survived about one hour and their blood alkali fell 78 per cent., while dogs succumbed in about thirty-five minutes and their blood alkali fell 75 per cent. In both animals the hydroxyl ion concentration fell 95 to 96 per cent. It is to be noted that in none of these experiments was the oxygen of the blood reduced.

These observations form the chief basis of the belief that acid intoxication kills by asphyxia of the tissue cells from accumulation in them of carbon dioxid. A partial dissent from this view is expressed by Loewy and Münzer, who believe that the production of carbon dioxid is diminished in acid intoxication; and this belief may be supported by the reduced consumption of many acid products of metabolism, resulting in lessened carbon dioxid formation, in diabetes. Beddard, Pembry and Spriggs found that the blood in diabetes is able to absorb a normal amount of carbon dioxid, even when its alkalinity and actual carbon dioxid content are greatly reduced. As a rule, the carbon dioxid tension of saliva and urine equals that of the secreting cells, but the above observers found that in diabetes the carbon dioxid tension of the urine is not increased. While the conception of cellular asphyxia is probably valid as far as it goes, further knowledge of the conditions determining the vitality of cells seems necessary before this theory can be regarded as proved.

Some other obscurities still surround the toxic action of acids. It has been surmised, but not satisfactorily proved, that vital organs are rendered seriously deficient in alkalies by administration of acids. An increased loss of alkali in the urine was demonstrated by Salkowski in taurin-poisoned rabbits, but he was unable to conclude that the loss was large enough to be serious. Schetelig found that the calcium oxid in the urine of acid-poisoned rabbits rose from 400 to 500 mg. per diem. From these and many other observations it is clear that acidosis is marked by considerable loss of alkali by the urine. But some of this urinary alkali is certainly diverted from the feces, which is the normal channel of 90 per cent. of the alkali excretion (von Noorden and Belgart).

Moreover, the body possesses practically inexhaustible supplies of alkaline earth in the bones, as well as very considerable resources in the food, and it still appears doubtful if these depots are not sufficiently available in acid intoxication to maintain the necessary alkali of vital tissues, while giving up those of the blood. The alkali content of such organs as the liver, kidneys and brain, in experimental acidosis, has apparently not been determined. It may be that the bone alkalies are not available in acute poisoning, in which alterations in these structures have not been found. In rabbits succumbing to large amounts of hydrochloric acid over a period of twelve days I could find no gross or microscopic changes in the bones. Yet in diabetes Frerichs states that the bones are abnormally light, and von Noorden concludes that the bone alkalies are extensively drawn on in diabetic acidosis. Gerhardt and Schlesinger

came to the same conclusion for severe diabetes, finding no other source for continuous loss of calcium in the urine. It is therefore probable that the bone salts are available in chronic acidosis, but not in the acute forms. On the other hand, the diseases associated with progressive loss of bone salts, rachitis and osteomalacia, have not declared themselves as forms of acid dyscrasia. There is a mass of clinical and experimental data indicating that the organs are rather susceptible to slight changes in their alkalies, but the pathologic significance of such changes in acid intoxication, especially in the acute and experimental forms, would be made clearer by accurate determination of the alkalies of the organs. According to Moore, the alkalinity of the tissues depends on interchanges of mono-sodium and disodium phosphates and by virtue of alterations in the relative amounts of these salts the cells may take up considerable quantities of acids without change in their reactions. Hence, Bainbridge supposes that by some interference with this protective mechanism of the phosphates and carbonates the tissues can no longer get rid of the acids produced and that their accumulation in the cells brings metabolism to an abrupt close. He regards it as extremely probable that the lack of some of these bases may disturb metabolism quite independently of the alkalescence of the tissues.

The method of estimating the alkalinity by the hydroxyl ion concentration has been applied to the blood by Szili and Benedict in Tangl's laboratory. They show that normal blood contains the same concentration of hydroxyl ions, that is, the same dynamic alkalinity, as distilled water. In animals poisoned by acid this concentration is reduced 95 per cent., so that this phase of alkalinity is practically obliterated. Physical and physiologic chemists will doubtless fail to agree on the significance of these observations, but they at least point to a new and interesting character of genuine acid intoxication, which may serve to separate true from spurious forms and thus prove a healthy control on the hasty application of the doctrine of acid intoxication. Landau holds that hydroxyl ions have little to do with blood alkalinity because they are derived from Na_2CO_3 and NaH_2PO_4, salts which ionize very slightly.

An important phase of the question of blood alkalescence has been revealed by the work of Rzentkowski. It has long been realized that the acid-neutralizing power of the blood, its basicity, depends not merely on alkalies, but is a function of alkalies, proteins, urea and other nitrogenous substances. By alkalescence may be understood that part of the basicity due to alkalies. Rzentkowski titrated separately with N/20 sulphuric acid and litmus, the whole blood, the plasma, and the cells, with the following results:

Acid-neutralizing power of the blood in mg. NaOH per 100.

	Whole Blood.	Plasma.	Cells.
Total basicity	387	165	560
Basicity due to alkali	160.8	137.6	172
Basicity due to proteids	226	27.4	388

These results indicate a remarkable preponderance of acid-neutralizing power in the red cells. This conclusion is by no means new, but Rzentkowski found that 1 gm. of red cell protein is equal to 12 mg. of sodium hydrate in neutralizing acids, while 1 gm. of plasma protein equals only 3 mg. sodium hydrate, and, regarding the unit of blood, he shows that red cells may neutralize four and one-half times as much acid as the plasma. The red cells owe their basicity to proteins, the plasma chiefly to minerals, and loss of basicity in red cells may be due not to loss of protein, but to qualitative changes in the protein, such as the capacity to split off ammonia. Hence, the effects of acids in the blood are very imperfectly measured by the loss of alkali and probably also by the loss of carbon dioxid. It is to be considered, also, if these results do not lessen the significance of the data obtained by estimations of the hydroxyl ion concentration, for here is a type of basicity which is only distantly connected, if at all, with hydroxyl ions.

In any case, it appears that the adherents of the acid-intoxication theory have been relying on very inadequate methods of determining the acid-neutralizing power of the blood. Since this tissue must probably first feel the effects of any excess of acids produced in metabolism, it is quite unwarranted to assume diminished alkalescence of other organ cells until that of the blood has been definitely proved.

VISCERAL LESIONS IN EXPERIMENTAL ACIDOSIS.

The pathologic anatomy of experimental acid intoxication occupies a subordinate position among the data relating to this condition. Salkowski took occasion to note that the liver in his cases of taurin-poisoning was not fatty. Some gastrointestinal lesions have been referred to the direct effects of the ingested acid. Usually the visceral changes have been dismissed with the statement of the accepted fact that no alterations capable of explaining death were observable.

With the object of ascertaining if any of the gross or minute visceral lesions were comparable to those observed in forms of supposed acid intoxications occurring in man, I have studied the anatomic condition in rabbits after rapid and prolonged poisoning by hydrochloric acid. Subcutaneous injection of N/8 to N/4 hydrochloric acid were employed throughout. This method was chosen on account of the gastric lesions produced by administration by mouth and the uncertainty of absorption

of the acid. The intravenous route, while suitable for very rapid effects, is not adapted to more prolonged experiments. Weak acids are very irritating to the peritoneum. I was unable to inject fatal doses of acid beneath the skin without producing considerable damage to this tissue and eventually exciting an inflammatory process which retards absorption. Stronger solutions than N/8 usually cause necrosis and suppuration.

A brief detail of some of these experiments follows:

RABBIT 1.—Black, male, weight 1,935 gm. Rapid subcutaneous administration of N/8 hydrochloric acid.

December 16: 12 m., 12 c.c. N/8 hydrochloric acid; 2:30 p. m., 12 c.c.; 5 p. m., 12 c.c. No symptoms.

December 17: 10 a. m., 12 c.c. N/8 hydrochloric acid; 12 m., 12 c.c.; 2 p. m., 12 c.c. N/4 hydrochloric acid; 3:30 p. m., 25 c.c.; 5 p. m., 25 c.c. Animal dull all day.

December 18: Animal died, 8:30 a. m.

Over a period of thirty-six hours the rabbit received, in divided doses, 60 c.c. N/8 hydrochloric acid and 60 c.c. N/4 hydrochloric acid. After the fifth injection the animal began to appear dull, and this symptom increased with the increasing strength of acid. No marked disturbance of respiration occurred. Death occurred fourteen hours after the last injection made at 6:30 p. m., at which time the animal did not appear to be seriously affected. Total acid received, 82 gm.

Autopsy.—Rigor, prompt, firm. Slight edema of subcutaneous tissue. Lungs very pale. Liver dark brown, no congestion or fatty degeneration. Kidneys appear normal. Stomach contains considerable food; shows no lesions. Intestine similar. Muscle pale. Bone marrow congested. Pia and brain appear normal.

RABBIT 2.—White, male, 1,720 gm.

December 18: Three injections, 12 c.c. each, N/6 hydrochloric acid. Rabbit appeared well; no symptoms.

December 19: Twelve injections, 12 c.c. each, N/6 hydrochloric acid. Rapid breathing noted after seventh injection. Later this became slow and shallow; ears cold, cyanotic; muscular twitching; very dull. Three hours after last injection animal much better.

December 20: Eating heartily. Red cells, 4,656,000; normal in appearance. Leucocytes, 7,500. Blood drop, cyanotic. Four hourly injections of 15 c.c. N/4 hydrochloric acid. Dull; head sways. Respiration, 48. One injection, 60 c.c. N/4 hydrochloric acid. Drowsy, cyanotic. Respiration unchanged. Thirty-five minutes after last injection, rabbit had a few general spasms and died. Total acid used, 2.16 gm. in fifty-two hours

Autopsy.—Blood dark, fluid. Marked general edema at point of injection. Lungs, anemic; other viscera congested. No signs of fatty degeneration. Liver, dark red. Bile, light green. Muscles pale; marrow congested. Brain normal. Bladder contains 40 c.c. clear urine showing a trace of albumin; very many hyaline casts; ammonia nitrogen 4.2 mg. in 100 c.c. (Dr. P. A. Shaffer).

RABBIT 3.—White, male, 2,060 gm. For four days received 15 c.c. N/8 hydrochloric acid; then for five days 30 c.c.; on tenth and eleventh days 60 c.c. each. Died during night of eleventh day. During all this time the animal was increasingly dull, but no respiratory disturbance could be detected.

Autopsy.—Weight 1,750 gm., loss 310 gm. Abdominal wall showed extensive edema and in places slight purulent infiltration. Blood, fluid, dark. Lungs congested. Stomach well filled with food. Kidneys pale. Liver dark-colored, congested, not fatty. Bile brilliant green. Muscle very pale. Spleen soft, of normal size. Brain negative. Bones everywhere of usual appearance.

Conclusions.—From these experiments two conclusions seem to be obvious: first, that rabbits withstand considerable quantities of acids slowly administered (one receiving 1,485 gm. in 11 days); and, second, that when the acid is slowly given subcutaneously, drowsiness is the chief symptom, and the characteristic dyspnea can be recognized with great difficulty, if at all.

Summary of Gross Appearance of Organs.—On account of the venous character and fluidity of the blood and the congestion of the viscera one would conclude that the cause of death in these animals was some form of asphyxia, which is also indicated by the symptoms. Yet the anemia of the lungs, skin and muscles, while consistent with slow asphyxia, is not characteristic of any common form of slow asphyxia seen in man. The brilliant green color of the bile deserves more than routine notice, since it indicates a pronounced acidification of this secretion which may, perhaps, be regarded as pathognomonic of this form of acid intoxication. Otherwise I can only confirm the conclusions of others, that the organs show no gross lesions characteristic of acid poisoning.

Microscopic Examination.—Material fixed in formalin. Orth's and Zenker's fluids yielded the following general data: 1. An entire absence of fatty degeneration in frozen sections of liver, and kidney stained by Sudan III. 2. A peculiar granular and hydropic degeneration of the liver and, to a less extent, of the renal tubule cells. The eosin-staining material in the cells appeared to be very deficient. In some foci and in many isolated cells of the liver the cytoplasm was represented by a thin cell border and a few stainable clumps of granules. 3. Swelling and hyaline transformation of many voluntary muscle fibers. 4. Absence of any alteration in appearance of compact and cancellous bone tissue. 5. Marked chromatolysis of stichochrome cells of central nervous system.

This last character recalls similar changes reported by me in 1898, in a case of acute hydrochloric acid poisoning in an adult man. While none of these changes can be regarded as pathognomonic, and while their interpretation presents many difficulties, I believe that they constitute evidence which may prove of value and which can not wisely be ignored in the diagnosis of other forms of acid intoxication.

Mossé describes a microchemical test for acidosis. In fasting animals, in uremia, and after death from various poisons, he finds that the liver fixed in alcohol and stained by the May-Grünwald method or by neutral red, shows a distinct basophilic tint. Heiberg obtained a distinct reaction of this sort in the livers of mice fasting for seventy-two hours.

Mice fed five days on meat and butter and killed twelve hours after a single meal of carbohydrate showed normal staining reactions of the liver. I find that livers of rabbits poisoned by hydrochloric acid, fixed in alcohol, and stained by Nocht's method, or by eosin and methlyene blue, stain densely blue and take little or no eosin; yet I doubt the wisdom of attaching much importance to slight variations in the staining reaction of material obtained at autopsy.

2. Acidosis After Extirpation of the Liver.

Another fundamental chapter in the rôle of ammonia in physiology and in the conception of acidosis concerns the relation of ammonia to urea-formation and to the functions of the liver.

It had previously been shown by Salkowski, Schmiedeberg and others that various ammonia salts administered to animals were not excreted as ammonia, but gave rise to increased excretion of urea and the conclusion appeared obvious that the ammonia was synthesized into urea. In 1886 Minkowski reported his remarkable observations on the influence on uric-acid formation of resection of the liver in geese, demonstrating that the synthesis of uric acid in birds is largely, if not exclusively, a function of the liver. The anatomic relations of the liver in birds permits the animals to survive, for about twenty hours, ligation of the portal vein, which diverts the blood to the inferior vena cava, the ligation of all arteries leading to the liver, and the partial or complete extirpation of this organ. In animals surviving this operation the excretion of nitrogen falls 50 to 60 per cent.; uric acid, the avian representative of urea, falls to one-thirtieth part of the normal excretion; the ammonia rises to 50 or 60 per cent. of the total nitrogen; while lactic acid, normally absent, reaches the enormous excretion of 3.5 gm. for twelve hours and constitutes one-half of the solid residue of the urine. The urine contains no sugar. The blood contains no sugar, but small quantities of leucin and tyrosin. On feeding these animals urea it was excreted as such, but amino-acids, glycocoll, asparagin, were largely broken up, with increase of ammonia, but partly excreted as such. That the excess of ammonia was not caused by its diversion to neutralize acid was shown by Engelmann, who, by giving alkalies, was able to reduce the ammonia without increasing the uric acid. The animals died in ten to twelve hours with vomiting, somnolence, coma, and occasionally with convulsions.

From these experiments several highly important conclusions could be drawn:

1. In birds the synthesis of uric acid (and urea) from ammonia is exclusively the function of the liver.

2. The appearance of increased ammonia in the urine may result from loss of the synthetic uric-acid-forming function of the liver.

3. The desamidation of amido-acids is possibly a function of the liver, but resides also in other tissues.

In order to determine how far the results in birds were applicable to higher mammals, direct observations on dogs were necessary. The partial or complete elimination of hepatic function in dogs has been accomplished by von Schroeder, by diverting the portal blood through a canula to a renal vein; by Hahn, Massen, Nencki and Pawlow, by means of an Eck fistula between portal vein and inferior cava, at times combined with ligation of the hepatic artery; and by Denys and Stube by injection into the bile ducts of acetic acid or by E. Pick with N/25 sulphuric acid. After all these procedures the animals rapidly passed into a state of intoxication marked by vomiting, thirst, somnolence, coma and convulsions. In animals with the Eck fistula the liver underwent fatty degeneration and atrophy, but collateral circulation was sometimes established and the animals survived. In these cases the symptoms were most striking, consisting of attacks of somnolence, muscular weakness and ataxia, followed by cerebral excitation, blindness, anesthesia and finally convulsions and coma. Feeding meat promptly induced an attack, sometimes fatal. The urine regularly showed a reduction in urea and excess of ammonia in combination with carbamic acid, and to the toxic action of this salt Nencki and Hahn chiefly attributed the symptoms. By the injection into normal dogs or by oral administration of this acid and its salts in animals with Eck fistulas they produced identical symptoms. In dogs with the Eck fistula the urinary ammonia nitrogen rose to 10 or 20 per cent., which is not very excessive; but it was noted that the ammonia increased rapidly with the appearance of toxic symptoms. In the brains of animals dead of this intoxication they found twice as much (20.5 per cent.) ammonia as in other organs (10.5 per cent.), and four times as much as in the brain of the normal dog (5 per cent.). Moreover, the arterial blood of a dog with an Eck fistula and toxic symptoms, contained as much ammonia as the portal blood of a normal dog.[2]

2. It may be noted here that carbamic acid (NH_2COOH) stands at the foot of the series of amido-acids $C_nH_{2n}(NH_2)$—COOH, and of the other amido-acids, as leucin, $C_5H_{10}NH_2COOH$, several are also present in these conditions. To what extent this or other acids of the series figure in the results of the Eck fistula and homologous conditions is not known. From this point of view it is possible to conceive of a special but in one sense spurious type of acidosis, constituted by the amido-acids, all of which involve combinations with ammonia.

In animals with the Eck fistula or in which the liver has been destroyed by injections of destructive agents in the bile ducts, the alkalescence of the blood is not apparently much reduced. No very complete observations on this point are available, but Denys and Stube and E. Pick failed to find any marked reduction in the alkalescence of the blood in their experiments. In this respect an important divergence exists from the conditions found in experimental intoxication by acids.

Salaskin and Zaleski find a striking difference in the results of extirpation of the liver from those following the Eck fistula or destruction of the liver by injection of acids into the bile ducts. With the Eck fistula the synthesis of ammonia into urea is defective; there is increase of ammonium carbamate in the blood and intoxication by this agent; the carbon dioxid of the blood is not reduced, and the urine is alkaline. After extirpation of the liver more complicated processes arise; the synthesis of ammonia into urea is defective; lactic and other acids are produced in excess with corresponding increase of ammonia; the carbon dioxid content of the blood is probably reduced and the urine is acid. Biedl and Winterberg were unable to verify some of the above observations, possibly owing to differences in technics, and, like Lieblein, they assert that ammonium carbamate is not directly concerned in these intoxications. While the exact details and interpretation of results may be left to future investigators, the significance of the observations of the Russian school need not be seriously doubted.

The studies in this field are of fundamental importance, not only for the physiology of nitrogenous metabolism, but for the doctrine of acid intoxication. They show that ammonia is essentially connected with the formation of urea and the functions of the liver, and that this urinary measure of acidosis may be increased by primary disturbance of hepatic function, in which an entirely secondary and theoretical acidosis exists.

When such a primary disturbance of the liver occurs, as from an Eck fistula, it is obvious that not only the urea-forming function, but all the other functions are disordered or abolished. Hence, the tendency to refer all the symptoms to the action of one agent, such as carbamic acid, must lead to grave error. It falls outside the scope of the present topic to consider in detail the biliary function, the relation to carbohydrate metabolism, and other phases of nitrogenous metabolism, or to dwell on the various symptoms accompanying disturbance of these functions, but it is probable that in hepatic disease associated with excess of urinary ammonia the influence of all these factors may have to be considered.

It has thus been shown by the foregoing lines of experimental research that:

1. It is possible to kill animals by injections of mineral acids or even of organic acids in large quantity, and such animals die with marked reduction of some of the acid-neutralizing properties of the blood and with diminished carbon dioxid content sufficient to explain their peculiar dyspnea. In such cases the urine shows marked reduction of urea nitrogen and corresponding excess of ammonia, which is diverted to neutralize the acids. The autopsy findings indicate death from asphyxia, and the organs are free from notable lesions.

2. When the functions of the liver are abolished, animals die with very pronounced nervous symptoms, extreme loss of urea nitrogen, high ammonia nitrogen, and the presence in blood and urine of carbamic acid and ammonia, the chief antecedents of urea, and with considerable lactic acid. The urinary signs of acidosis are pronounced and in many respects similar to those seen after experimental acid poisoning, but in the case of the Eck fistula no increased formation of acids has occurred, no abstraction of tissue alkali can be assumed, and death must result from some different mechanism, possibly from intoxication with accumulating antedecedents of urea. The autopsy shows nearly complete destruction of the liver, secondary degeneration of other organs, but little reduction of blood alkalescence or carbon dioxid content. After extirpation of the liver more complicated processes arise, marked by increase of lactic acid and by excess of ammonia from failure of urea synthesis and probably from diversion of ammonia for the neutralization of acids.

Armed with these two striking pictures furnished by experimental pathology one may now safely enter the field of clinical medicine, to ascertain to what extent these prototypes are reproduced by spontaneous diseases of man and lower animals.

3. Clinical Development of the Doctrine of Acid Intoxication.

In 1857 Petters showed that the penetrating odor of the breath, urine and organs of diabetic subjects is caused by acetone, and he first referred the coma of diabetes to acetone poisoning. Later Kaulich demonstrated acetone in the urine of many diabetics and described a group of nervous symptoms as a characteristic clinical picture of acetonemia. This substance was subsequently found in the urine in many other conditions, some of which showed no nervous symptoms, and opinions became divided regarding the significance of acetonemia, some holding that it was the cause of the terminal intoxication of diabetes and of nervous

symptoms in many diseases, others believing that it possessed little or no important clinical significance.

Kussmaul was very direct in his criticism of the idea of acetone intoxication. He pointed out that acetone had long been used in the treatment of phthisis and that in considerable quantities it was entirely without toxic effects in man. In a case of advanced phthisis he administered 4 gm. daily for six weeks without noting any of the symptoms described by Kaulich. He tested the toxicity of acetone in rabbits and dogs and concluded that it was much less toxic than chloroform and slightly more so than alcohol, which it closely resembled in action.

Kussmaul's Coma.

In 1874 Kussmaul drew attention to the peculiar clinical features of certain cases of diabetic coma and sharply distinguished them from those of Kaulich's acetonemia. These features were:

1. A characteristic form of dyspnea. The respiratory movements were very deep, regular, *grosse Atmung,* and somewhat accelerated, 20 to 40 per minute. The movement of air was entirely unobstructed and venous congestion of the jugular veins during life and of the viscera after death was absent. The contrast between the general weakness and the deep, powerful respiration was most striking.

2. A rapid and weak heart action, 120 to 140 per minute.

3. Nervous excitation, restlessness, screaming, jactitation and hypogastric pain.

4. Coma, beginning one or more hours after the appearance of dyspnea and continuing till death. The temperature, slightly elevated at first, became subnormal and the pupils were normal or contracted.

Kussmaul concluded that this form of coma was caused by a direct stimulus of the respiratory center by some intoxication arising in the course of the disease and not from loss of oxygen, or accumulation of carbon dioxid, or from acetone poisoning.

Von Jaksch's Acetonemia.

The next advance in the study of diabetic coma was furnished by R. von Jaksch, who, in 1883, showed that Gerhardt's ferric chloric reaction in febrile and diabetic urines was referable to diacetic acid. Although, as Folin points out, von Jaksch was dealing with a mixture of diacetic and beta-oxybutyric acids, this was the first demonstration of acid substances in the acetone series. Instead of bringing the observation in line with the excessive urinary ammonia in diabetes, von Jaksch firmly believed in the direct toxic action of acetone and diacetic acid,

and he constructed an elaborate classification of the various clinical forms of acetonemia.

Another characteristic of diabetic urine which required explanation was the high proportion of ammonia demonstrated by Hallervorden. In one case he found 5.96 gm. of ammonia excreted in one day, an amount equal to 60 c.c. aqua ammonia and equivalent to 17.18 gm. of concentrated sulphuric acid. A parallel between the excretion of ammonia and the intensity of the disease appeared not to exist. Hallervorden accepted the view that the ammonia signified neutralization of acids and he administered 45 gm. of sodium bicarbonate with the idea of replacing the ammonia, but the experiment failed to prove the theory, as the ammonia remained unaltered.

Discovery of Oxybutyric Acid in Diabetes.

It was an essential contribution to the subject when Stadelmann, by balancing the known acids and bases, proved that diabetic urine contains a great excess of bases over that required to neutralize the inorganic acids, and hence that some unknown organic acid must exist in the highly acid diabetic urine. He attempted to isolate the acid and obtained a substance free from nitrogen and sulphur which he regarded as crotonic acid, CH_2CHCH_2COOH. He drew the further important conclusion that diabetic coma of Kussmaul's type is identical in character with that produced by Walter by ingestion of hydrochloric acid in rabbits, and that it must be, therefore, an acid intoxication, and he announced his determination to treat his next case of coma with sodium carbonate.

Stadelmann's work was promptly followed by the demonstration, simultaneously by Külz and by Minkowski, of beta-oxybutyric as the questionable acid in diabetic urine. Besides beta-oxybutyric acid and its derivative, diacetic acid, which may be regarded as of similar significance, diabetic urine is said to contain other organic acids which may figure in the intoxication. Reckoning acetone as diacetic acid, from which it is rapidly formed in the urine, the total quantity of diacetic acid in coma seldom reaches the maximum observed by Magnus-Levy—33 gm. in a case giving 120 gm. beta-oxybutyric acid. Usually acetone and diacetic acid are much less in amount, so that they usually contribute a very small part of the acidosis.

Traces of lactic acid have been found (Rumpf), but they may result from fermentation of sugar. The sarcolactic acid of Minkowski was probably a terminal or postmortem product. Volatile fatty acids were isolated by von Jaksch and by Rumpf, but Magnus-Levy criticizes the

methods employed and believes that such products are chiefly derived from changes in beta-oxybutyric acid. If present as such the quantities are trifling, so that diabetic acidosis is almost entirely due to diacetic and beta-oxybutyric acids.

While the majority of observers at this time were rather firmly convinced that the dyspneic coma of diabetes was the result of abstraction of alkalies from the blood and tissues, a true acid action, von Jaksch and others held to the theory of a "coma diaceticum" caused by direct toxic action of acetone compounds and it was generally acknowledged that decisive proof had not been furnished for either theory. It was especially the comparative resistance of carnivora to acid poisoning and the demonstration by Coranda that man resembles the dog in his feeble response to ingested acids that established a serious doubt, not yet entirely removed, that a fatal acid intoxication could ever arise spontaneously in the course of disease in man.

Clinical Studies of Oxybutyric Acid in Diabetes.

In the minds of many the final evidence in favor of the acid intoxication theory of diabetic coma has been furnished from the clinical side, whence alone it could come, by numerous quantitative estimations of the excretion of acetone compounds in a series of cases. On such observations in diabetic coma must rest the final verdict regarding the significance of this form of acidosis, for in no other conditions are the acetone compounds present in such quantity and nowhere else do characteristic symptoms seem so definitely connected with acidosis.

The earlier observations indicated that beta-oxybutyric acid or the sum total of acetone compounds in diabetes were formed in considerable but not in really large quantities. Stadelmann calculated from the excess of urinary bases that 8 to 23 gm. of the acid measured the daily excretion in his case of coma. Minkowski, after the administration of alkali, found 24 gm. on the day of fatal coma. Wolpe, in nine cases, found an average of 5 gm., but 23 gm. appeared in a comatose patient. He could not establish a parallel between the ammonia and acid excretion. Later Minkowski found that an excretion of 16 gm. daily had risen, after three weeks, to 53 gm. during coma. On the other hand, Baumann obtained only 10 gm. from 1½ liters of urine passed during the final forty-eight hours of coma.

The most extensive report on the quantitative excretion of beta-oxybutyric acid is that of Magnus-Levy, and many believe that the enormous quantities which this observer has found in certain cases has furnished the final proof of the acid intoxication theory of diabetic coma.

While beta-oxybutyric acid is absent in mild cases of diabetes, Magnus-Levy concludes from more than thirty subjects that this acid is present in all severe cases of the disease and tends to increase as the disease progresses, ranging in cases free from coma from 7 to 30 gm. daily. Yet he reports one severe case progressing unfavorably in which only traces were found, and his and other reports show great variations in the amount of acid excreted. In coma very much larger amounts appear, especially with alkali treatment. In one remarkable case (VI) the enormous quantity of 157 gm. of beta-oxybutyric and diacetic acids was estimated from the excess of bases over inorganic acids in 92 liters of urine. In another case 107 gm. were found, or 4 to 4.5 gm. per kilo of the patient's weight. Yet in four cases coma appeared when the excretion of acids ran from 20 to 40 gm. and one instance (II) coma developed when only 2.5 gm. were found.

It is clear that the very large quantities of acid recorded in these reports were largely referable to excessive diuresis from sodium bicarbonate. Yet the acid was present in the body, and Magnus-Levy calculates, with what validity is uncertain, that in a patient weighing 30 kg. and excreting 143 gm. of beta-oxybutyric acid, fatal acidification of the body would be produced by 80 to 150 gm. of the acid. However uncertain such computations may be, it is obvious that the quantities of organic acids in diabetic urine are far beyond any reasonable limit of safety.

The relation to symptoms must be determined, however, not solely from their presence in the urine, but from evidence of their existence and action in the body. From Magnus-Levy's table, considered merely as statistics, it is possible to argue that the coma was caused by glucose or ammonia, quite as much as by beta-oxybutyric acid, for all these substances were enormously increased by the alkaline diuretic. It is necessary to inquire to what extent the other features of Walter's acid poisoning are represented in diabetic coma.

The alkalescence of the blood, as measured by the carbon dioxid content, was found by Minkowski to be 30 volumes per cent. in normal human arterial blood, 1.17 volumes per cent. in a diabetic subject free from coma, and 3.3 volumes per cent. some weeks later during coma. At the same time the venous blood showed 19.5 volumes per cent. (1,000 mm. pressure). Kraus in thirteen cases found the carbon dioxid in venous blood (at 760 mm. pressure) from 10.20 to 19.77 volumes per cent. (normal, 35 to 40 volumes per cent.).

The titratable alkali of the venous blood was determined by Kraus in a fatal coma and found to have fallen to 125 mg. sodium hydrate for 100 c.c. of blood, normal 185 to 220 mg.

Magnus-Levy, using Löwy's method, found that normal blood yielded an alkali value almost never less than 260 mg. sodium hydrate, and seldom more than 400 mg., while this alkalinity was not greatly reduced in any other condition except diabetic coma. In mild cases of diabetes the alkalescence was found within normal limits. In three severe cases coma began with normal alkalinity (361, 290, 324 mg.), but fell during its progress to 234 and 124 mg. and in one case recovering under alkalies it rose from 324 to 362 mg., falling to 154 mg. in the blood five minutes postmortem.

These results with the carbon dioxid content and alkalinity of the blood, while far from demonstrative, may be regarded as consistent with the theory of acid intoxication.

In the blood and organs considerable quantities of beta-oxybutyric acid have been found which, especially in conjunction with other acids, may at least partially account for the reduced alkalescence. Minkowski determined the presence of over 0.22 per cent. of the acid in the blood of the cadaver. Magnus-Levy analyzed the blood and organs of three cases, finding as much as 0.22 per cent. in the blood, 0.14 per cent. in liver, 0.17 per cent. in spleen and 0.13 per cent. in the muscles, besides acetone, diacetic and lactic acids. In a patient of 45 kg. weight he calculated that the beta-oxybutyric acid amounted to 100 gm. Assuming an average fall in blood alkalescence in fatal coma of 220 mg. sodium hydrate (Löwy's method) he calculates that this could be produced by 572 mg. of beta-oxybutyric acid per 100 c.c. blood, which amount was actually found in the blood by Hogounenq.

ALKALI THERAPY IN DIABETIC COMA.

The results of alkali therapy further extend the parallel between diabetic coma and Walter's acid poisoning. The results of the practical test of Stadelmann's suggestion that the acid dyspneic coma might be combated by neutralizing the acids with alkalies were entirely unsuccessful, both in his own hands, with Hallervorden, who anticipated him, and with his immediate imitators. Patients in coma or excreting large amounts of ammonia failed to improve when given 20 to 40 gm. of sodium bicarbonate. When the quantity of alkali was increased better results were obtained. Magnus-Levy failed to abort fatal coma in three of four cases, although one of them received 200 gm. of sodium bicarbonate, but in a boy of 13 years he appeared to succeed in aborting two

attacks of coma by the enormous quantities of 210 and 200 gm. on the day of severest symptoms, although the urine remained acid. It is, of course, uncertain how severe these symptoms would have been without treatment.

In a second case, a child of 12 years, 100 gm. sodium bicarbonate was followed by the excretion of 7 liters of urine with 107.6 gm. of acid, and by marked improvement. Minkowski also reported one case of coma cured by alkali and Grube describes complete recovery from a definite coma in one adult with similar treatment.

In recent years reports and opinions regarding the efficacy of alkalies have varied greatly and failures certainly far outnumber the successes. Naunyn, in a recent review, states that in fully developed cases, intravenous injection of alkali does not relieve the coma, but at most causes temporary improvement. Before the outbreak of the coma, however, the results are much better. He was able to abort three attacks, but failed in the fourth occurring in the same patient.

The successful results seem to occur only in young subjects and in these, although some attacks may be influenced, later ones are fatal. Naunyn could report no case of coma in an adult cured by alkali. Although a consistent advocate of the alkali treatment, he freely admits that the good results may be due to other than the acid-neutralizing properties. In Young's case coma subsided for eleven days after venesection and injection with salt solution. Hilton-Fagge relieved another by infusion with the acid mixture sodium chlorate and sodium phosphate! In Naunyn's experience, 777 cases, the regulation of the diet with judicious use of carbohydrates seemed to be equally effective. Schwarz asserts that he cured by gluconic acid a case resisting alkali. Here the antiketogenic influence of this acid was supposed to come into action.

Finally it is admitted that dyspneic coma may develop during the administration of alkali and while the urine is alkaline, that is, when enough alkali is present to protect the tissues. In this connection it need not be overlooked that alkalies have themselves no inconsiderable tendency to increase the formation or excretion of acetone compounds.

THEORETICAL CONSIDERATIONS.

Are there any explanations which may account for these conflicting data and still leave the theory of acid intoxication a tenable hypothesis? Numerous efforts have been made to lighten the obscurities in this field with a success variously estimated by different authorities.

1. It may be maintained, first, that there are several types of coma in diabetes. Naunyn describes three, briefly indicated as: (a) Typical

acid dyspneic coma; (b) coma of doubtful type suggesting acid intoxication with severe acidosis; (c) coma of the same type without severe acidosis. One may, therefore, suppose that the cases which resist alkali are not the acid type of coma and that diabetic coma is not always of essentially the same origin. The majority of clinicians, however, are probably represented by von Noorden, who hesitates to accept this subdivision of the essential coma of diabetes. They prefer to suppose that the acid element of the coma is of necessity relieved by alkali, but that other contributing factors are uninfluenced.

2. Another line of argument is based on the possibility that the alkali when administered may not reach the acid in time or in sufficient quantity to neutralize it. A secondary hypothesis supposes that the acids before neutralization cause in the organs changes which themselves prove fatal, even after the acids are neutralized. The validity of these hypotheses can be estimated only by a minute consideration of the place of formation and the source of beta-oxybutyric acid, and it is not probable that in the present state of our knowledge a definite conclusion can be reached. Any acids derived from the fats and proteins of the blood or immediately reaching the blood from the tissues must be neutralized promptly by circulating alkali, when this is introduced intravenously, or even when administered by mouth, unless absorption is greatly retarded. It is not probable that acids from this source can cause any great loss of tissue alkali during alkaline treatment. Much the same condition must hold for the acids produced in the muscles.

Magnus-Levy conceives the acids as forming within organ cells and streaming into the blood plasma, but not before abstracting the fixed alkalies of the cells, which are thereby damaged, even in the presence of abundance of alkali in the blood. Hence, the alkali would be entirely effective only when present within the cells. From this quite hypothetical point of view it seems possible to explain the failure of the alkali therapy in the presence of a purely acid intoxication. In fact, while animals poisoned by acid *in extremis* react promptly to the injection of alkali it is a wonder that any one should expect the human body suffering from spontaneously forming intracellular acids to react in the same decisive manner.

Landau finds that in rabbits showing acidosis from phosphorus poisoning, administration of alkali has no effect on the total blood alkalescence, owing to the rapid excretion of the alkali by the urine, which becomes alkaline, and continuous formation of acids from toxic destruction of tissues. In fasting rabbits, in which the acidosis is referable to sulphuric and phosphoric acids and not to acetone compounds, sodium carbonate

promptly brings the blood alkalescence to normal and is able to hold it there, since in starvation acids are not so rapidly produced. Such considerations reveal some of the necessary limitations of alkali therapy in disease. At any rate, it must be accepted as a fact that diabetic coma is seldom or never cured by neutralization of acids, although it is probable that coma may be improved or even postponed by alkali therapy.

Against the purely acid nature of diabetic intoxication the objections seem to be far more direct.

1. There is the well-attested fact that coma closely resembling the dyspneic type may occur with little or no acidosis (Münzer and Strasser, Lépine, Kraus), but there seems to be insufficient ground for assuming that the condition is essentially different from that of the more typical cases. In Münzer and Strasser's case diacetic acid and acetone were present in abundance, but beta-oxybutyric acid was absent and no acetone compounds could be found in the blood of the cadaver. Magnus-Levy expresses the opinion that these observations are unreliable. In Magnus-Levy's Case 5, typical acid coma on one day was relieved by alkali, but recurred the next day without the dyspnea, yet Magnus-Levy believes that on the two days it was of identical origin.

2. Coma may improve when the urine still remains acid (Magnus-Levy) and may remain unaffected when the urine becomes alkaline.

3. The ammonia excretion, which is supposed to measure the degree of acidosis, does not run parallel with the quantity of acids as determined by other methods, and administration of alkali may not reduce the percentage of urinary ammonia.

It seems to be a still debatable question whether Kussmaul's dyspneic coma is specific of diabetes and acid poisoning.

Litten long ago described typical Kussmaul's coma in scarlatinal nephritis and, under the title "coma dyspepticum," he described very similar features in cases of marked gastric disturbance. Senator concluded that dyspneic coma occurs in other fatal diseases, as pernicious anemia and cancer, in which it is not associated with marked acidosis. Herzog also has recently pointed out the difficulties of distinguishing between diabetic and other forms of coma.

4. The ingestion or infusion of alkali has other prominent effects in addition to that of neutralizing acids. It is actively diuretic. In Magnus-Levy's most striking case of recovery from coma under alkali treatment, 220 gm. sodium bicarbonate in forty-eight hours increased the urine 273 per cent., the sugar 330 per cent., the organic acids 220 per cent. When the urine is increased from 2.6 liters to 7.1 liters it is

clear that opportunity has been given during this violent washing of tissues for excretion of many other noxious substances besides acids.

From the figures in this remarkable case taken without reference to the nature of the substance concerned we might suppose that the enormous output of sugar relieved the patient more than the removal of acids. Lépine believes that the alkaline treatment does good, not especially because it neutralizes acids—for the sodium salts of propionic, butyric, and lactic acids are toxic—but largely because it is diuretic.

It is on the physiologic action and not on the amounts of the substances excreted that the significance of the table depends.

Benedict adds to the obscurity of the subject by the results of observations on the hydrogen and hydroxyl ion content of the blood in diabetic coma. It was shown by Szili that the hydroxyl ion concentration of the blood, while identical with that of distilled water, is nevertheless reduced 95 per cent. in animals dying from injections of hydrochloric acid, in other words, that it is acid as determined by this method. Benedict, however, finds that in diabetes with severe acidosis the concentration of hydroxyl ions usually varies within normal limits. In coma it may be slightly diminished, but it is not far from the normal and is not lowered nearly as much as in other conditions in which symptoms of intoxication are absent. Farkas and Scipiades in two cases of normal pregnancy found lower readings for the hydroxyl ions than were obtained in Benedict's case of fatal diabetic coma. It may well prove, as Folin surmises, that physical chemical laws governing the solution of electrolytes are of little significance in pathologic physiology, and yet the fact remains that Benedict has brought to light a new point of difference between diabetic coma and experimental acid poisoning, and one that can not be lightly dismissed without further explanation.

5. The carbon dioxid content of the blood is greatly reduced in acid coma, but Meyer and Kraus find it greatly reduced in other conditions which are not marked by Kussmaul's signs, viz., in poisoning by many hemolytic agents, in miliary tuberculosis and erysipelas. Kraus also reports three cases of diabetic coma in which carbon dioxid content was very slightly altered, diacetic acid absent, and yet the symptoms could hardly be distinguished from dyspneic coma. These results suggest the need of repetition of the studies in the carbon dioxid content of the blood.

Finally it is a fact of frequent verification that patients may long withstand a severe acidosis, that coma frequently supervenes with diminishing excretion of sugar and ammonia, while Naunyn refers to a case which for six years withstood pronounced acidosis with the aid of alkalies, but finally died in coma in spite of them. All these observations seem

to indicate that there is some essential process which is responsible both for the acids and for the coma, and that a successful therapy must attack this earlier process.

In spite of the prodigious labor devoted to the subject over a period of thirty years, it is evident that the existence of an acid intoxication has not been placed beyond the field of debate. So many uncertainties still surround this question that nearly all of those who have carefully considered the available evidence have declined to take a positive stand on either side, and regard the matter as undetermined. The question is so complex and its phases reach out into so many branches of medical and collateral science as to suggest that the final verdict must await further progress in all departments. The practical value of the theory as a basis for hopeful therapeutics is its strongest plea for acceptance and here, at the same time, is presented its most potent weakness.

It is my personal opinion that the experimental basis of the theory of acid intoxication is sufficiently well founded and the chemical studies of diabetes furnish adequate grounds for concluding that acid intoxication produces coma in diabetes, but the clinical evidence is quite unsatisfactory. The clinical data point to the occurrence of identical symptoms in other conditions and even in diabetes in which there is comparatively little evidence of acidosis, while coma fails to develop with many diabetics with very severe acidosis. These facts appear to me irreconcilable with the assumption of an exclusively acid origin of diabetic coma, and lead me to think that acidosis is one of several factors leading to this coma, but one which stamps it with certain peculiar qualities.

The status of the whole subject of acid intoxication appears to depend on its position in diabetes. On this point Magnus-Levy is especially emphatic, asserting that in diabetic coma alone true acid intoxication exists; in all other conditions there is, in the sense of Naunyn, only physiologic acidosis.

All may not agree with this conclusion, but it is clear that in no other condition does the acidosis reach the same intensity as in diabetes. Yet the enormous amounts of beta-oxybutyric acid found by Magnus-Levy stand almost alone, and it is desirable that his results should be verified by independent observers.

It is equally clear that the direct attack on the problem by observations on human diabetes, on the results of alkali therapy, and on the experimental production of acidosis, have not succeeded in reaching a solution. More fundamental knowledge of the occurrence, source, chem-

istry, and physiology of the acetone compounds is needed before the correct interpretation of diabetic acidosis can be attained, and to the numerous contributions in this field attention may next be turned.

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(To be Continued.)

HYPERNEPHROMA.

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The curious tumor of which this paper treats, is one that has aroused an immense amount of interest, as well as some controversy, among the pathologists of the world. In Europe, particularly, has the neoplasm been studied and all its types described. In this country, the paper by A. O. J. Kelly, published in 1896, remains the most important and is the basis of most of the American work on these tumors. To examine the text-books treating of renal tumors is to see the confusion the varieties of hypernephroma have created in the minds of authors.

On account of the varying morphology of these growths, pathologists have described them under such different titles as angiosarcoma, perithelioma, papillary adenocarcinoma and cystoma, clear-celled epithelioma, spheroidal-celled carcinoma, alveolar endothelioma, sarcoma, adenoma and adrenal adenoma. Each observer seems to have excellent ground for his opinion; because, as a rule, the diagnosis is based on scant material, often on one case. In but few tumors are there so many and diverse microscopic pictures presented, and yet there is a generic similarity so striking that any experienced observer can identify them at a glance.

This variation in histologic structure is manifest not only in different examples of the growth, but in different areas of the same specimen; hence the necessity of studying long series of the tumors to determine the constants and variants, in order that the true tissue picture may be fixed in the mind. After such a study, the growth becomes a wonderfully individualized tumor type, and its vagaries are no longer confusing to the student. All the departures from the classical plan of construction can readily be explained when one becomes familiar with the accidents of growth, vascularization and degeneration that habitually occur in examples of hypernephroma. In the series before me are most of the varieties described in the literature.

For many years the small islands of adrenal tissue beneath the capsule of the kidney have been observed, and it has been the common inference that the renal hypernephroma springs from these adrenal rests. The

arguments to support this view are based on anatomical, chemical and histological grounds and seem valid, yet specimens that clearly demonstrate the situation are certainly rare. In the writer's observations of material in the collection of the University of Chicago, not a single specimen was found that was satisfying on this point. In fact, in but one specimen known to the writer does the origin from the ectopic adrenal seem clear, and that specimen is in the collection of the Northwestern University Medical School. This case will be discussed later.

It is not well to overlook the possibility of other sources of origin. It is a well known fact that in some cases of morbid growths of the thyroid gland that are structurally simple, adenomata give rise to metastases of tumors whose structure is very similar to normal thyroid. In an article in the last edition of the Reference Handbook of the Medical Sciences by H. G. Wells on the thyroid gland, mention is made of the tumors originating from the thyroid, some of which have a wonderfully close resemblance in structure and behavior to the tumors originating from adrenal tissue. Some of these tumors are in structure simple adenomas, yet they metastasize in the bones, lungs, liver and kidneys. The peculiar disposition they have of invading the veins is also seen in the hypernephromas. In Case 13 of the writer's series, it seems not unwarranted to infer the possibility of transference of adrenal cells through an aberrant blood vessel extending from the adrenal to the tumor.

In forming a conception of these neoplasms, it is well to begin with the study of the apparently normal bits of adrenal gland enclosed in the kidney capsule. Figure 19 shows these deposits to be perfectly normal adrenal cortex. In the most typical adenomatous tumors the only marked deviation from the normal histologic type is a simple broadening of the columns of parenchymatous cells. The regular alternation of blood vessel and cell column is well shown in Figure 24. A step further and the broadened cell columns soften in the center and we see a picture resembling an irregularly walled tubular gland (Fig. 25); or, if distension from fluid occurs, the picture becomes that of a papillary cyst (Fig. 23). In some cases, the softened center of the cell columns admits blood, and we are confronted with a picture of a perithelioma or angiosarcoma (Fig. 21).

The most unusual type is probably the fatty hypernephroma, which has been discussed recently by Keenan and Archibald. These tumors are simply hypernephromas whose parenchymatous elements are replaced by fat-cells. This transformation seems to depend on a very weak vitality of the tissues invaded. In one case of the writer's series is a specimen which has become segregated from its blood supply and has mummified.

Fig. 1 shows the dead nodule in the kidney. Weil says that the cystic variety of hypernephroma is simply a greatly degenerated example of the more hemorrhagic types of the tumor. Case 14 of the writer's series is well on the way to become a cystic hypernephroma.

The histologic aspects are hardly less remarkable in respect to variations than the gross morphology (Figs. 20 to 25).

Some few cases of these tumors have been reported in England as having occurred in children who were the victims of obesity and excessive growth of hair. These cases may represent a curious effect on metabolism effected by some perversion of the internal secretion of these tumors, thus indicating their relationship to tumors or adenomas of the hypophysis and thyroid and differentiating them physiologically from all other malignant tumors, since no carcinoma or sarcoma has any such specific effects.

Many authorities bring up the question of the production of arteriosclerosis by the adrenal secretion and it is a very common observation that patients dying of hypernephroma have an extreme degree of calcareous degeneration of their blood vessels. In Case 13 of this series an unusual degree of calcareous degeneration existed. The superficial vessels of the thorax looked like twisted pipe-stems under the skin, and were broken between the fingers with an audible crackle. The long history of this case, and the lack of destructive malignancy displayed by the tumor during a very long period of its existence, suggests the possibility of chronic adrenal intoxication with consequent arterial degeneration.

A considerable amount of chemical work has been done on these tumors, and some peculiar reactions have been described as specific. Croftan claims that a watery extract of these tumors injected into dogs and rabbits produces glycosuria, that it converts uncooked starch into dextrose and maltose, and that it decolorizes boiled starch stained with iodin. The writer has subjected all the tumors reported in this paper to the last two tests and found the reactions described in every case. Control tests with other neoplasms have constantly failed. Thus it seems that the chemical properties are no less interesting than the microscopical and clinical features.

So far as the writer knows, adrenalin has never been manufactured from the tissues from these tumors. Wells has found that the proportion of fat, lecithin and cholesterin present in hypernephromas corresponds closely with the proportion and amount found in normal adrenals, and is quite different from the fat and lipoid content of other tumors.

The general clinical features, the mode of metastasis, and the urinary findings, have all been so elaborately described in the later literature that the writer will omit these details and proceed to report a series of cases.

REPORT OF CASES.

CASE 1.—*History.*—Mr. F., aged 69, business man. This man had been for years past in good health, though very spare of build. Twenty days before coming under observation he attempted to push a heavy window up with a push stick. The implement slipped and threw the patient with some violence against the window-sill. This gave him great pain in the right loin, the part struck. He went to his home that evening complaining of the pain. That night he noticed blood in his urine. In the urine there were noted long cylinders of clotted blood. There appeared, on the subsequent days, great pain in the region of the right kidney and along the right ureter. Spasm was of frequent occurrence preceding the expulsion of the ureteral blood casts. Relief was sudden and complete after the clots passed. There were no casts in the urine at any time.

Diagnosis.—A surgeon was consulted ten days after the appearance of the hematuria, who diagnosed renal stone and advised operation. Consultants suggested the possibility of traumatic rupture of some renal vessel.

Treatment.—Operation was performed by Dr. J. F. Binnie. The right kidney was split and careful search was instituted for stone or ruptured vessels. Nothing of the kind being found, the kidney was drained and left alone. Ten days later the patient died, apparently from exhaustion and loss of blood, as the hematuria had persisted and further operation was refused.

Autopsy.—The postmortem was performed by a medical student who was nursing the patient and no careful examination made, simply the kidneys being secured and brought to the writer.

The right kidney was found slightly lengthened, being 21 cm. long. In the upper pole and to the posterior side was a flattened oval tumor that extended to the center of the kidney, invading the pelvis by a slender tongue. The renal vein was not preserved. The color of this tumor was light buff, variegated with brown and margined with a very dark, almost black, color. The substance was pulpy, but not necrotic. The tumor seems sharply marked off from the renal substance by a fairly defined capsule of shining white sclerotic tissue. The entire tumor was broken up into spherical masses of varying size by bands of fibrous tissue.

The histologic structure of this tumor is as follows: At first glance there appears, under the lower power, a great expanse of moderate-sized, clear cells, having large, vesicular nuclei variously placed; the cells seem to occupy elongated alveoli separated from each other by a delicate connective tissue stroma. Under the high power, the cells are seen to be attached to these septa of connective tissue, the first rows seeming to be in a better state of nutrition, as they stain deeply with eosin, while the rows far removed present distended cell-walls and an almost colorless cytoplasm. Indeed, in many places, the areas farthest away from the connective tissue base are showing unmistakable signs of granular disintegration and liquefaction, leaving the area presenting the features of a cyst lined with several rows of epithelium. The examination of the stroma shows this to be made up of a central capillary blood vessel supported by a few strands of connective tissue. Here and there, at broad intersecting or junction points, are aggregations of small round cells.

It is evident that the tumor is one whose parenchyma rests on scantily clad capillary blood vessels, and that all the varying features are the result of a cell proliferation in excess of the nutrition furnished by the vessels, and, as the soft-

ening of alveoli of cells takes place, pseudo-cysts are formed. Otherwise one might, if looking at certain sections, pronounce the growth a cystic adenopapilloma. The dark emargination of certain of the nodules is seen to be due to blood pigment that is being carried away from the tumor by carrier cells. The relation of cells to blood vessels, and the character of the nuclei and bodies of the parenchymatous cells, closely resemble the same features of the adrenal; hence the diagnosis of hypernephroma.

CASE 2.—*History.*—J. C., aged 41; operated on by Dr. J. F. Binnie, Oct. 24, 1902. Five years ago, had an attack of almost painless hematuria. General health at that time perfect. After an interval of several months, had another attack in which the flow of blood was very profuse and attended with pain in the left renal region with reflection to the inner side of left thigh. The pain was finally relieved by the passage of a long round clot. The urine almost immediately cleared of blood and the patient felt in perfect health. After this time the hematuria recurred every few months, with the same history of relief from pain after the passage of the clot from the ureter. After the last seizure the patient determined to seek surgical relief, and accordingly consulted Dr. Binnie. It had been two months since the last severe attack of pain.

The urine was sent to the writer and presented the following features: Sp. gr. 1018; reaction sharply acid; color, slight tinge of pink; albumin, a good trace; sugar, none. Microscopically, it presented many red blood cells, some tailed epithelial cells, a few leucocytes and many dumb-bell uric-acid crystals. No casts or other evidence of nephritis. There are many bundles or strings of fibrin.

Diagnosis.—Diagnosis of stone suggested.

Operation.—At the time of operation the patient looked well and hearty. No temperature; pulse 85 and of normal volume. Exposure of kidney through lumbar incision showed a good-sized, yellowish, tuberculated mass occupying the upper pole of the left kidney. This was thought by the surgeon to be a localized renal tuberculosis, and the affected portion was resected, leaving an apparently normal lower two-thirds of the organ in place. The patient reacted well, and everything seemed to be doing well for twenty-four hours. Then the pulse began to rise, and at the end of twenty-four hours the radial pulse was so fast that it could not be counted. The face was blanched and the respiration rapid and jerky. The patient died about forty-eight hours after the operation with the rapid pulse, peculiar respiration and without temperature or local signs of any kind.

Autopsy was refused.

Pathologic Findings.—The specimen received by the writer is a multinodular, sulphur-yellow neoplasm, measuring 6 cm. in diameter. The tumor is covered over most of its surface by a thin capsule. The remaining portion is raw, and it is evident that the knife divided the mass through tumor tissue, leaving the remains in the situation of origin. The cut surface shows, for the most part, cross-sections of rough spheres of an intensely yellow pulpy tissue. Here and there are areas of brown, granular substance, evidently old hemorrhage. The paths of connective tissue that divide the tumor into the bosses, so evident on the surface and in cross-section, are very white and clear, like a soft cartilage.

Microscopic sections show the tumor to be made up of numerous thin filaments of connective tissue, in the center of each of which is a capillary blood vessel; resting against these vascular fingers of tissue are broad tunics of large, clear, flask-shaped epithelial-like cells. They are extremely irregular in size and shape, and each cell seems to be trying to get a surface contact with the vascular support; this has the effect of drawing out some portion of many of the cells into long stems that insinuate between cells having broader contact surfaces. The nuclei of the cells are very large and possess nucleoli that take the eosin

intensely. The chromatin in the nucleus is more abundant next to the nuclear membrane and takes the hematoxylin well, thus showing the acidophile nucleolus in good contrast. Not a single cell was found in karyokinetic division. At the region farthest away from the blood vessel the cells are in some confusion and show evidences of granular degeneration. Here red blood cells are finding their way, also many polymorphonuclear leucocytes.

It is easy to see that the center of these broad columns of cells will degenerate and permit a stream of blood to flow through them. Indeed, this very thing is found in several of the sections of this tumor. Such a field looks like a venous angioma with the vessel wall lined with great clear cells instead of flat endothelium. Tumors of the type presented here would be recognized with difficulty, from the sections alone, as being derived from the adrenal structure. Their yellow color in the gross, and the regular alternation of capillary blood vessels and cell columns, are features that the adrenal presents in common with these tumors. There is no other organ in the human body that presents just these features. This particular case presents the broadest cell columns of any in the writer's series of specimens. Figure 25 is a fairly average field.

Diagnosis.—Hypernephroma of the fasciculate variety.

CASE 3.—*History.*—Mrs. X., aged 45; operated on by Dr. G. W. Lilly, of Kansas City, Mo., 1889. Twelve years before the date of the operation, had suffered for several months from pain in the left kidney and an intermittent hematuria. Ever since has had more or less pain in the kidney. She was, at the time of the operation, thin and extremely nervous, but had no hematuria.

Diagnosis.—The diagnosis of latent renal tuberculosis was made and operation advised. This was agreed to, and accordingly the operation was done. The specimen was preserved in alcohol and presented to the writer by Dr. Lilly three years after it was removed.

Pathologic Findings.—The tumor occupies the upper pole of the left kidney and was invisible until the organ was sectioned. The tumor is roughly spherical, measuring 6 by 4 cm., and is completely separated from the kidney substance, falling out of its bed like a nut out of the hull. Microscopic examination of the tumor tissue shows a well-preserved topography, though the nuclei of the cells do not take the stain. The section takes a light eosin stain, with here and there a very pale outline of a cell nucleus. The cell bodies are seen to be large and bladder-like, and rest two or three deep on very slender dendritic fingers of connective tissue containing blood vessels. In a few of the broader paths of stroma are the slits in the tissue where cholesterin crystals have dissolved out in the preparation of the sections. The picture is typically that of an ordinary hypernephroma. The kidney substance stains distinctly, so that it is fair to presume that the tumor tissue was, indeed, dead at the time it was removed with the containing kidney.

Since its removal, the patient has lost much of the apprehensive fear that caused so much of her nervous trouble. Her general physical condition is the same as before operation. Figure 1 shows section of the kidney.

CASE 4.—*History.*—Mr. X., aged 50, laborer; patient of Dr. Froeling, Kansas City, Mo., 1902. The case history contains nothing of interest antedating the present illness, which began with vague gastric symptoms about a year previous to his admission to the hospital. At the present time, the man is very thin and cachectic. Complains continually of gastric pain and discomfort. Temperature normal; pulse not recorded. Gastric analysis shows no free HCl and no Oppler-Boas bacilli. Gastric fluid reported as typical of pyloric obstruction. The patient died before any operative procedure was attempted.

Autopsy.—The postmortem was performed by a medical student, who complained to me that he could find no right kidney, but that the liver was the seat

of a fibrous tumor. On examination I found the lower aspect of the right lobe of the liver the seat of an oval tumor that measured 12 by 9 by 9 cm. It was welded to the surface of the liver by a tough pinkish connective tissue. The cut section of the tumor was firm and for the most part consisted of white glistening fibrous tissue. Here and there was an oval area of softer tissue of a yellowish color. There was no kidney tissue to be found. The duodenum was involved in the same tissue that bound the tumor to the liver and was entirely covered to the pylorus by a tunic, about one-half inch thick, of this fibrous tissue. The pyloric opening was very small from the contraction of the duodenum. The lymph nodes about the hilum of the liver were similarly covered, but did not seem to be otherwise involved. No metastases were found in any other viscus of the body.

Microscopic Examination.—Sections made from the tissue of the ovoid tumor that represented the kidney, showed a very extensive mass of spindle-celled tissue that might easily be mistaken for a spindle-celled sarcoma. These spindle elements are arranged in the whorled fashion so often encountered in fibromata and spindle-celled sarcomata. Here and there, however, is an area of typical hypernephromatous tissue. The cells in these areas are large, clear, irregular bodies, with large vesicular central nuclei, resting two or three cells deep on a delicate finger of supporting tissue. The center of the thin strip of stroma is almost always occupied by a thin-walled capillary. The tissue that constitutes the

Fig. 1.—Photograph, one-half size, of Case 3. The tumor mass is seen as a dry, yellowish nodule lying free in a cavity in the upper pole of the kidney. There seems to be no vascular connection whatever with the kidney. The tumor mass is dead. Sections show unstainable cell bodies.

cementing adhesions between the tumor and the liver is purely the spindle-celled connective tissue. There are many places where this tissue is invading the true hepatic tissue, after the fashion of a sarcoma. The entire duodenum is plastered over to a thickness of almost a centimeter by this same spindle-celled tissue. No trace of hypernephroma tissue can be found on the intestine.

CASE 5.—*History.*—Mr. C., aged 68, farmer; operated on by Dr. J. W. Perkins at St. Margaret's Hospital, Oct. 12, 1905.

Clinical Diagnosis.—Sarcoma of the head of the left humerus. Family history contains nothing of interest in connection with the case. Personal history is as follows. He had been a very healthy and vigorous man all through life; had no serious illness of any kind. In December, 1904, had a fall on the left shoulder and suffered what was thought to be a dislocation. Reduction was attained, but the shoulder remained swollen and stiff. Great pain was continuously experienced in the head of the bone. Loss of flesh was very noticeable and progressive. A few months later, the patient accidentally found that a tumor had appeared deep in the right gluteal region. Both tumor masses have slowly enlarged and

are now painful to pressure. The patient was seen by me a few days before the operation, and the diagnosis of metastatic hypernephroma suggested.

Examination at this time showed a very thin man presenting a good-sized globular tumor in the head of the left humerus. On grasping the tumor so as to encircle it with the hands, a very distinct pulsation could be felt. A thin capsule of bone covered the tumor. This crackles on sharp pressure, like the thin bony capsules of myeloid sarcoma. The tumor in the right gluteal region was evidently located in the ileum near the crest. It pulsated also.

Fig. 2.—Photograph, half-size, of specimens from Case 4. Shows the intimate adhesion of the tumor mass to the under surface of the right lobe of the liver. This tumor is extremely fibrous. The upper end of the duodenum is shown and the tag of tissue at the top is turned to show the thickness of the tunic of fibrous tissue that covers the entire duodenum.

Diagnosis.—The diagnosis of myeloid sarcoma was a hard one to refuse, but was discredited because of the rare occurrence of secondary bony metastases of that tumor. The rapidity of growth of the tumors was also contrary to the usual slow development of myeloid sarcoma. Careful search was instituted for evidence of kidney tumor, but without success. The urine gave no clue whatever.

Operation.—The arm was amputated at the shoulder and the specimen brought to the laboratory.

Pathologic Findings.—The head of the humerus is almost globular in shape. The affected portion measures 9 by 4 by 5 cm. The marrow cavity at the neck

of the bone is completely filled with a soft, brain-like tissue that is variegated bright yellow and brown. The cancelous bone of the head of the humerus is invaded by masses of the tumor, but not totally replaced. The bone at the neck is completely destroyed and the tumor tissue is in contact with the muscles and fascia. The bony tissue that is not destroyed is as thin as paper.

Microscopic examination shows the most perfect histologic picture of hypernephroma. The entire tumor mass is made up of an infinite number of capillary blood vessels, looping so as to form a multitude of irregularly oval and elongated spaces. These spaces are occupied by great clear cells that are resting on the capillary loops. The mimicry of vegetable cells is wonderfully close. The nuclei are all round and of almost exactly the same size. The nucleolus is very large and takes the eosin intensely, making it stand out conspicuously against the light blue of the nucleus. There are a few hemorrhagic areas in the tissue, but no hyaline degeneration or thick sclerous connective tissue, so common in the

Fig. 3.—Photograph of specimen from Case 5. Head of the left humerus split open. Shows the tumor occupying the marrow cavity and producing a pathologic fracture at the neck of the bone.

tumors in the kidney. The diagnosis of hypernephroma can be made without any serious doubt. The patient made a recovery from the operation and left the hospital. He died two months later at his home out in the center of Kansas, and no postmortem was obtained, so that we will never know the origin of the tumor. The specimen is shown half-size in Figure 3.

CASE 6.—*History.*—Mrs. X., German housewife, aged 47; operated on by Dr. Gray, Oct. 1, 1907, at St. Margaret's Hospital, Kansas City, Kan. History previous to present illness negative. Three months before admission to the hospital she had an attack of anuria. This was accompanied by great pain in the right renal region and persistent nausea and vomiting. The attending physician discovered a tumor in the right side just below the liver. The anuria lasted twenty-four hours and was followed by the passage of a ureteral blood clot and a copious hematuria. All the symptoms of pain were immediately banished. During the

three months that intervened before the operation, the patient continued to lose flesh and became anemic. There were no more hemorrhages from the kidney so far as the patient knew.

Operation showed the right kidney to be the seat of a tumor. No extensions of the growth were revealed by the examination at that time, and the kidney was removed.

Pathologic Findings.—The specimen presents a growth that measures 13 by 10 by 9 cm., affecting the upper pole and extending to the pelvis of the organ. Its surface is made up of a series of oval bosses that nowhere penetrate the capsule of the kidney. The color is yellowish, with the cut surface marked out into oval and round areas by white translucent fibrous tissue. The tumor nodules in many instances are pulpy from the formation of minute cystic cavities. There are areas that are quite dark from old extravasation of blood. The renal vein seems free from invasion. The pelvis is invaded by a single tongue of tumor tissue.

Fig. 4.—Photograph of specimen from Case 6. Shows the commonest type of hypernephroma, a yellowish lobulated soft mass replacing the upper pole of the kidney and invading the pelvis.

Microscopic section shows the tumor to be made up of small cells that in most of the section are closely packed and show no definite arrangement. In certain areas, however, the cells are somewhat larger and are arranged on the walls of thin blood vessels. Here the cells are mere thin-walled, clear globules with a large, round, eccentrically placed, pale-staining nucleus, the typical hypernephroma arrangement. At those places where the cyst is found, the arrangement is like a papillary cystoma; the contents of the cysts is evidently formed from the disintegration of the parenchymatous cells, as there are many of the distended cells free amid the granular material. A few of the cysts are occupied by washed-out red blood cells. The connective tissue of this tumor is in varying stages of hyaline degeneration and is full of small round cells. One area in the tumor is particularly soft and yellow; here the cells are much larger and cover the blood

vessels several cells deep; the nuclei are very large and contain large nucleoli that stain intensely with the eosin; the cell protoplasm is filled with fine pink-staining granules. Some of the cells show about the nucleus fine yellow pigment, while here and there, both in the stroma and in the parenchyma, are cells whose protoplasm is filled with large spherical granules that take the eosin intensely. These granules I take to be related to, if not identical with, Russell bodies. This tumor is a very typical hypernephroma in the gross (Fig. 4). It is interesting microscopically in the variation of the histologic picture in different portions of the growth. Inquiry made of the physician who furnished this case, as to the final outcome, brings out the fact that the patient died some months later of liver disease, nature unknown.

CASE 7.—*History.*—L. C. C., aged 56, married, ranchman. Case of Dr. J. W. Perkins, Kansas City, Mo.

Clinical Diagnosis.—Hypernephroma of the right kidney. Parents died at the age of 70 years. Brother and sister died at about 40 of tuberculosis. Patient had no sickness except a bronchitis that came on in the winter. Last summer he had an attack of nausea and vomiting that lasted for two months. Eight years ago had an attack of hematuria that lasted about two weeks. No further bleeding into the urinary tract occurred until April, 1905, since which time more or less blood has been noted in the urine. On several occasions distinct and copious hemorrhages appeared. Slight pain was felt along the crest of the right ilium all the time. This pain at intervals became acute. His back had for some time felt weak and at times painful. Constipation since 1905. Confined to the bed a great part of the time since June, 1905. Feb. 26, 1906, urine presents red blood cells, abundant; staphylococcus; no tubercle bacilli; no casts or other evidence of nephritis. Physical examination shows patient an elderly anemic man; no particular cachexia. In the right iliac fossa is a large movable tumor that gravitates to the median line when the patient lies on the left side. Pressure over the tumor produces distinct pain. Patient was confined to bed and the urine soon cleared of the blood. After a month of rest and quiet the blood again began to appear in the urine, at first in great quantity, but gradually diminishing until the operation, which was undertaken March 16, 1906.

Fig. 5.—Photograph of specimen from Case 7. Shows an unusual position of the tumor on the anterior surface of the kidney. Apparently began about the hilum. Tumor rather firm and covered by very large blood vessels. Pelvis invaded by soft polypoid mass of tumor tissue, shown at lower portion of picture. Very profuse hematuria in this case.

Operation.—Excision of the right kidney through the anterior route. The tumor was found to be attached to the kidney and was about the size of the kidney and much the same shape. The tumor seemed to infiltrate the kidney substance for some distance. The renal vein was carefully lifted and cut close to the vena cava. The vein for quite a distance out of the kidney was filled with a soft cylinder of the tumor tissue. The patient was very weak during the operation, suffering severe shock.

Postoperative History.—Six hours after the operation there was passed two ounces of bloody urine. After this, the urine cleared up, and the patient thereafter passed about one pint daily during the period of convalescence. He was troubled much with gas pains for several days. March 23 a bronchitis appeared, that was attended with a temperature of about 102 F. Drainage from the wound was profuse for several days. March 26 there was a severe vomiting attack, accompanied with great distention of the bowels with gas. This state of affairs

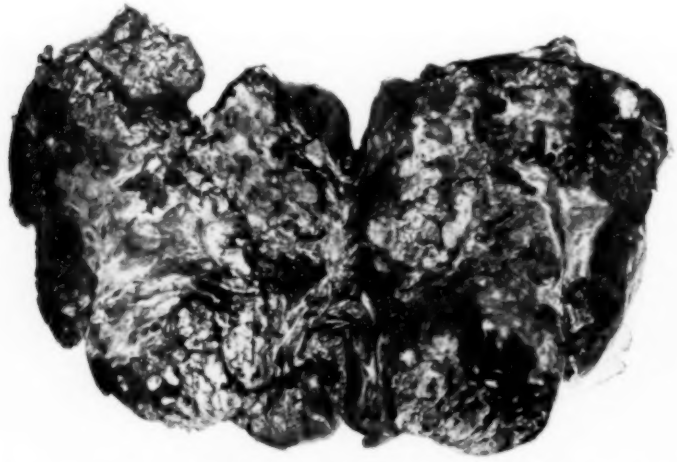

Fig. 6.—Photograph of specimen from Case 8. Half size. This specimen illustrates well the usual aspect of the more rapidly developing soft types of hypernephroma. There are many large extravasations of blood shown in the dark areas of the photograph. This type often breaks down into a cyst filled with softened tumor tissue, blood, and necrotic fragments. Fluid from such a pseudocyst generally contains much cholesterin, in addition to the débris from the blood and tumor.

continued. The feces were thin and offensive. March 30 his temperature dropped to subnormal and the patient seemed in collapse. April 2 was the first time the patient could retain food. The diarrhea then checked. On April 6 he sat up in bed; April 11 was in a wheel-chair; April 14 walked; April 21 about the hospital, well on the way to recovery.

Blood Examination.—Red cells, 2,875,000; leucocytes, 17,100. May 7 discharged, with the operation wound almost closed. On Feb. 11, 1907, a letter was received from this patient, stating that he had gained forty-eight pounds in weight and was in fine health.

Microscopic examination of the tumor shows it to be made up of a relatively large amount of poorly fibrillated stroma, enclosing oblong and irregularly oval areas of very large clear cells. So clear are the cells that the nuclei seem to hang suspended in the center by the finest web of very lightly staining substance. The cells look much like vegetable cells. Here and there are giant cells with very large irregularly outlined vesicular nuclei. In many places in the stroma are collections of lymphoid cells. There are a few hemorrhagic areas. No degenerated areas are noted; the nutrition of the growth seems perfect (Fig. 5).

Macroscopically, the specimen presents a broad attachment to the anterior surface of the kidney. The surface is slightly lobulated, firm and surrounded by a firm capsule of fatty connective tissue. It measures 10 by 8 by 6 cm. and, together with the kidney, weighs 410 grams. The cut surface shows much glistening fibrous tissue, dividing the tumor into many oval and circular areas of soft, bright yellow tissue. Near the capsule are several small areas of dark brown color, evidently areas into which blood has escaped. At the surface of the kidney

Fig. 7.—Photograph of specimens from Case 9. The left kidney almost entirely occupied by a soft broken down hypernephroma; the right kidney shows the upper pole occupied by the solid, bright yellow type of hypernephroma, with the pelvis and renal vein occupied by a soft polypoid extension of the growth.

there is a sharp line of demarcation, as if the tumor had originally been independent of the kidney. The tumor projected a tongue of its substance into the pelvis and also into the renal vein, the latter being 2 centimeters in length. These projections are much softer and of a brighter yellow than the tissue in the body of the tumor.

CASE 8.—*History.*—H. H. M., aged 65, married, business man. Case of Dr. J. W. Perkins, Kansas City, Mo. Operated on May 9, 1906. Clinical diagnosis: Hypernephroma of the left kidney. Antecedent family history presents nothing of interest. In 1870 had typhoid fever. Two years ago had rheumatism in the muscles of the hip. Two months ago had obstinate constipation, for three days during which he suffered from nausea and vomiting. The last two weeks there has been very annoying frontal headache that always begins early in the morning

and lasts till noon. Ten days ago noted the urine tinged with blood. The hematuria became severe and continuous up to two days ago. One month ago the tissues about the cheeks and neck, scrotum, legs and thigh became distinctly edematous. One year ago there was noted by the patient a small lump in the left side, two inches below the ribs, and in the axillary line. He paid no attention to this, as there was no pain present. At the present time there is a tumor in the situation named, a large mass bulging both forward and backward. It is covered by slightly darkened skin. There is no pain elicited on moderate manipulation or pressure over the mass.

Operation.—Done May 9, 1906; excision of the left kidney and attached tumor through the anterior route. The tumor presents a soft, cheesy appearance (Fig. 6). The hemorrhage was large and the patient was exhausted when removed from the table. Large drainage tube was left in for three days. The patient rallied perfectly and in a few days was clamoring to get up. The recovery was uneventful and the patient was discharged on June 2, 1906.

CASE 9.—*History.*—Mrs. B., aged 65, housewife. Operated on by Dr. C. Lester Hall, 1906.

Fig. 8.—Specimen from Case 10. Remarkable in that the tumor axis is transverse to that of the kidney. The mass seems to be attached to the pelvis. The renal vein and pelvis were both extensively penetrated by polypoid masses of tumor tissue.

Clinical Diagnosis.—Renal tuberculosis. Nothing in the family history of direct interest. For three years she has noted an enlargement in the region of the left kidney. Her general health began to decline markedly two years ago, at which time she suffered with marked gastric disturbance and epigastric pain. She vomited a great deal. There was nothing in the vomitus that could be attributed to any definite stomach disease. Diagnosis of reflex vomiting made by family physician. Urine about this time contained much pus and débris and occasionally blood. There have never been profuse hemorrhages from the urinary organs. At all times during the last year there has been a low fever. Some attacks of rather acute pain in the region of the tumor have made the patient faint. At times she has complained of great pain in the back and legs. For the past few months the patient has been very debilitated.

Operation.—With the diagnosis of renal tuberculosis the operation of nephrectomy was attempted, but the patient died on the table before the operation could be concluded. The kidney was removed, together with its fellow on the right side, for pathologic examination. Both organs are the seat of hypernephroma (Fig. 7). A rather casual examination was made of the abdominal contents and no tumors were noted in the other organs. Unfortunately, a complete postmortem was refused.

Pathologic Findings.—The left kidney is a soft mass measuring 17 by 10 by 9 cm. There is a small fragment of kidney substance at the lower pole. What remains of the pelvis is dilated into a very irregular cavity that contains turbid urine. The color is almost a uniform pinkish yellow. The numerous round areas of tumor tissue are very spongy in texture, and softening of many of them is notable. There is a minimum of hemorrhage into the substance of the tumor.

Fig. 9.—Photograph of specimen from Case 11. The specimen is the largest and most rapid in growth of all the specimens of hypernephroma observed by the author. The tissue is soft and bright yellow, with a minimum of connective tissue. There was neither renal vein involvement nor invasion of the pelvis.

Microscopically, the tumor nodules are made up of a scanty stroma, well vascularized. The parenchymatous cells are rather small vesicles, with round vesicular nuclei containing large, pink-staining nucleoli. They are arranged on the walls of very thin capillaries in layers two to three cells deep. There are relatively wide spaces remaining in each nodule that are not occupied by the parenchymatous cells, but by a granular semi-fluid substance, admixed with cholesterin plates. The general low power aspect of the sections is that of a cystic papillary adenoma. The arrangement of the cells on thin fingers of connective tissue bearing a central capillary, and the clear flask-like cells with metachromatic nucleoli, make the diagnosis hypernephroma.

The right kidney presents at its upper pole a solid bright yellow tumor extending from the capsule to the pelvis. There is a fine cylindrical tumor extension projecting four centimeters into the renal vein. The figure sufficiently illustrates the gross aspect without a written description (Fig. 7).

Microscopic section shows a solid tumor, totally devoid of the cystic spaces presented by the tumor of the left kidney. The cells are arranged a dozen or so thick on a base made up of little save a thin-walled capillary. The type of tumor is exactly the same as that presented by Case 2. Cases of bilateral hypernephroma are evidently rare, as I have been unable to get track of but one other case reported in English, by Le Count, of Chicago.

CASE 10.—*History.*—Mrs. O. B., housewife, aged 41. Operated on by Dr. J. D. Griffith at St. Joseph's Hospital, Jan. 10, 1907. Clinical diagnosis: Hypernephroma of the left kidney. Health excellent until delivered by forceps, July, 1904. Worked at household duties, but under difficulties, until March, 1906, since which time she has been unable to work on account of pain in the back and lower abdomen. Became pregnant in November, 1906, and was delivered of a dead

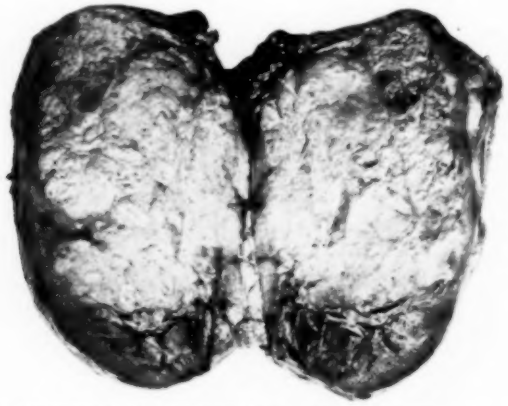

Fig. 10.—Photograph of specimen from Case 12, reduced to one-third the actual size. The specimen is of the usual type of hypernephroma.

child at the eighth month. Following this confinement she had chills and fever and had remained bedridden until January, 1807. Physical examination revealed a large, sharply projecting tumor below the costal arch on the left side. The tumor was movable to a slight degree. The urine contained blood, a few leucocytes, but no casts. Patient complained of pain on urination, the cause of which was never discovered.

Operation resulted in the removal of a tumor of the upper pole of the left kidney.

Pathologic Findings.—The tumor presented its long axis transversely to the axis of the kidney, the pole of the kidney blending with the tumor mass at the middle. The mass measures 15 by 9 by 10 cm. and is itself almost the exact shape of a kidney. The color of the tumor is bright yellow with variegations of brown. The capsule is fairly thick and covers many hemispherical nodules of the tumor that project as much as a centimeter above the general surface. The capsule contains an unusual number of large, tortuous blood vessels coursing over

the surface of the growth. The consistence is elastic. Cut section shows a fairly solid tumor mass of yellow and brown tissue, marked into oval and round areas by connective tissue. There are no cystic cavities, and only a fair amount of extravasated blood. The tumor mass penetrates the pelvis of the kidney and there is a short plug of tumor tissue in the renal vein. This is the only example of this tumor seen by the writer, at right angles to the axis of the kidney (Fig. 8).

CASE 11.—*History.*—Mrs. C., negress, aged 39. Operated on by Dr. W. J. Frick. Referred to surgeon by Dr. Mackey, of Odessa, Mo. History was difficult to obtain and very meager. The patient is a mulatto in good state of nutrition. Three months ago she was delivered of a full-term child. Shortly after this she

Fig. 11.—Photograph of tumor from Case 14. Shows well the large spherical type of hypernephroma, that is so disposed to central softening, and the formation of a cyst filled with grumous material and cholesterin crystals.

noticed a tumor in the left side. This was painless and fixed in its position. The mass rapidly grew until the abdomen was as large as before delivery. There was never any particular pain associated with the growth or reflected to other regions. No blood was found in the urine at any time. Her general health was fair. Bowels constipated.

Diagnosis.—No closer clinical diagnosis could be made than abdominal tumor.

Operation through the abdomen. The growth was covered by very large blood vessels. The vascular capsule was thin and non-adherent. The tumor was elastic. Unusually large veins entered the tumor at the inner face. These were tied

off and the tumor lifted from its bed. No remains of the kidney were noted at the time of operation. The patient made an uneventful recovery. One year later she died after four weeks of fever that was diagnosticated typhoid, and from all that the writer can learn from the attending physician this diagnosis was correct.

Pathologic Findings.—Tumor measures 20 by 13 by 9 cm. and occupies the entire kidney, there being but a shell of renal tissue covering the lower aspect of the tumor. The texture is soft and granular, the color is a dark yellowish brown. There are a few well-marked hemorrhagic areas through the substance. There is a single blunt cone of tumor tissue projecting into the pelvis, but it is completely covered by the pelvic mucosa. The renal vein escaped invasion.

Fig. 12.—Photograph, two-thirds natural size, of specimen from Case 15.

Histologically, the specimen is very interesting in that the mass is almost wholly cellular. The cells are disposed in exceedingly thick tunics on a core of scant connective tissue containing a thin-walled capillary. The cells themselves are of the most irregular description, but conform in general to the clear flask type so common in these tumors. There are many large areas that are occupied by syncytial masses of clear protoplasm, containing very large and irregular nuclei. There are also many cell inclusions to be seen. The nucleoli are universally extremely large and stain intensely with the eosin. There are many beautiful karyokinetic figures to be seen throughout the tumor.

This is the only specimen in the series before the writer that contains any division figures. The type of karyokinetic division seems to be very degenerate, there being many of the tripolar figures, and in many of the very large cells the skeins of chromatin seem to be exploded, the fragments distributed throughout

the entire cell body. The evidence of rapid cell division and the rapid growth of this tumor makes the recovery of the patient very remarkable. This, of all the cases here reported, presents the greatest histologic malignancy.

CASE 12.—*History.*—Mrs. Julia G., housewife, aged 39. Operated on at St. Margaret's Hospital, Feb. 15, 1905. Diagnosis: Tuberculosis of right kidney. Father died of an accident at the age of 52. Mother died of malaria at 68. Very fragmentary, but the following interesting scraps were gathered together. She was operated on at St. Margaret's Hospital, Kansas City, Kan., by Dr. Perkins twelve years ago and had both ovaries removed. Operated on by Dr. Perkins six

Fig. 13.—Photograph, one-third natural size, of a hypernephroma from the kidney of a cow (Case 16).

years ago for perinephritic abscess. Three years ago she returned with the sinus still discharging and had a curettement of the sinus. Examination of the urine shows some pus cells and red blood globules, but no tubercle bacilli. The general health of the patient is fair. She is very nervous, but shows no marked disability in other ways. The kidney was removed by the lumbar incision and the specimen sent to the writer for diagnosis.

Pathologic Findings.—The specimen consists of a right kidney enclosing a tumor mass that almost fills the organ. It measures 14 by 9 by 7 cm. The surface is firm and shows numerous bossated projections over the surfaces. The capsule is nowhere broken. There are numerous dilated and very tortuous vessels

coursing over the surface. Cut section shows the kidney substance almost entirely replaced by a friable yellowish tumor mass. A softer, blood-stained group of spherical nodules occupies the upper pole. The pelvis is almost completely obliterated by extensions of the neoplasm. There is none of the renal vein attached to the specimen. The right adrenal gland is imbedded in a mass of loose tissue adhering to the kidney. The adrenal gland seems normal. Microscopic section shows a typical hypernephroma of the fasciculate type.

CASE 13.—*History.*—G. C. E., aged 56, painter; hypernephroma with general abdominal extension; died at St. Margaret's Hospital, Kansas City, Kan., Jan. 9, 1907. Postmortem on the same date. No history of previous illness of any character. Two years ago he developed great pain across the upper portion of the abdomen. At intervals of a few days he had attacks of vomiting. At this time he was thought to be "leaded," and the abdominal pain and vomiting were attributed to lead poisoning. During the past six months he has lost forty pounds in weight. During the past few weeks the vomiting and pain have lessened to a great extent. During the entire time since the abdominal pain commenced there has been a steady decline in health. Constipation has been very persistent and has given great trouble. There has been no edema, cough, or other suggestive symptom until two months ago, when a full tumbler of almost pure blood passed from the bladder. For several days after the urine was tinged with blood. Ex-

Fig. 14.—Photograph, reduced about one-third, of a kidney from a man 45 years old, showing an ectopic adrenal. The normal gland was in place and of proper size.

amination of the urine shows no morbid products except some red blood cells. Examination of the patient shows a large tumor mass occupying almost all the space in the upper portion of the abdomen. There is rather more prominence on the right side than toward the median line. The mass is immovable and great bosses of tumor can be felt through the thin abdominal walls pretty much all over the abdomen. No change in the thorax was noted, except a pronounced upward displacement of the liver. The skeletal system is normal so far as can be made out.

Pathologic Findings.—Autopsy done by Dr. Frank J. Hall, Jan. 9, 1907. Body that of a greatly emaciated man about 57 years old. Skin yellowish, dry and inelastic. Rigor mortis poorly marked. Scarcely any lividity. No marks of disease on the skin. Tissues very dry. Entire upper and middle portions of abdominal cavity occupied by a tumor mass. No fluid in the cavity. The tumor mass crowds the transverse colon close beneath the diaphragm and the small intestines into the pelvis. The liver is shoved entirely beneath the ribs. There are no tumor masses in any of the abdominal organs, except the right kidney, which is completely involved in a great reddish yellow bosselated mass.

CASE 14.—*History.*—Mr. W., aged 59, farmer: hypernephroma of the right kidney; operated on by Dr. Jabez N. Jackson, Kansas City, Mo. Present illness began two years ago, when patient noticed that stooping over produced an acute pain in the right side, at the margin of the ribs. At the same time a small lump was discovered in the region of the right kidney. This lump gradually became more evident. As the tumor grew, the patient thinks that the urine diminished in amount. When walking, the pain in the back would be so great that the patient would have to sit down to avoid fainting. He became increasingly constipated and passed much gas from the bowels. Belching seemed to relieve the

Fig. 15.—Photograph of the cut section of the kidney from Case 17, showing the section of the tumor, presenting in the center an oblique section of a large blood vessel filled with lighter colored tumor tissue. The following figure shows the vessel continuing out of the tumor and entering the left adrenal.

sense of abdominal tension. He had to sleep on his back all the time, as any other posture produced acute pain in the right side and even over the abdomen. Headaches have been of frequent occurrence. For some time the increasing yellowing of the skin had been noted with alarm by the patient. At night there have been frequent attacks of shooting pain in the bottom of the right foot. Similar pains have been felt in the testes and penis. Right testicle at the time of operation

was about three times the size of the normal. The testicular pain is relieved by the sitting posture. Has noted that the referred pains are more severe at the times that the urine is dark in color. The active loss of flesh began about eighteen months ago. At the time of severe pain the urine is very dark, but is perfectly clear at those times when pains are absent. At the time when trouble began, he had attacks of pain every two months or thereabouts, then the period shortened to two weeks, then every few days, and now there are attacks every day. The pain begins at the margin of the ribs on the right side and progresses downward to the penis or foot. Urinary examinations made recently show a normal urine,

Fig. 16.—Photograph of outer surface of kidney of Case 17, with left adrenal. The figure shows the aberrant blood vessel issuing from the left adrenal and coursing over the surface of the renal tumor and entering the tumor mass at its junction with the kidney. After entering the tumor the vessel is found filled with the oldest of the tumor tissue, which is well shown in the preceding figure as lighter in form. The left adrenal is not the seat of a definite neoplasm.

except for fresh red blood cells, which are constantly present, but in varying quantity.

Operation.—The kidney was removed through the abdomen and sent to the laboratory, where the diagnosis of hypernephroma was confirmed.

Pathologic Findings.—The specimen is a very fine example of this species of tumor (Fig. 11). It is spherical in shape and covered with the same capsule as

that enclosing the remains of the kidney. The tumor affects the upper pole and measures 13 cm. in diameter. The cut section resembles a sectional grape fruit, as the pulpy tumor tissue is roughly separated by opalescent bands of connective tissue that radiate from the center. The entire tumor is of a light yellow color, but certain areas near the capsule are of a bright canary color. Some of the peripheral areas have been infiltrated with blood and are consequently of a dirty brown color. The entire center of the growth is evidently on the verge of breaking down. Had this occurred the tumor would then have been a thin-walled cyst instead of a tumor, as there is so small an amount of living or well-nourished tissue at the periphery of the growth.

Fig. 17.—Photograph showing the atheromatous aorta and the surrounding mass of lymphnodes filled with tumor tissue. The contraction from sclerosis is extreme (Case 17).

Microscopic sections made from different portions show the tissue in the well-nourished portion to be made up of a fine mesh of capillaries, supporting broad tunics of perfectly clear cells, with large round nuclei. The cellular mass is of the "vegetable cell" type in great purity. In the degenerated areas there is nothing left but cell débris and hyaline connective tissue.

CASE 15.—*History.*—Mr. X., aged 45; hypernephroma of the right kidney; operated on by Dr. O. J. Cunningham of Kansas City, Mo., Dec. 10, 1904. In 1892 the patient was under the care of Dr. J. D. Griffith of this city. At that time he complained of a tumor in the right side, of several months' duration. There had been two or three attacks of sharp pain in the right flank that were

relieved by the passing of clots and blood from the bladder. Operation was performed, but the growth was regarded as inoperable. The operative diagnosis was sarcoma of the kidney and retroperitoneal tissues. The patient made a good recovery and left the hospital. After the lapse of about two years of increasing difficulty the patient applied for surgical aid again. Since the first operation there have been seven hemorrhages into the bladder every two or three months. In these attacks the patient nearly died from loss of blood. At other times he passed in the urine jelly-like clots that almost occluded the urethra. At all times red cells could be found in the urine microscopically. The patient says that the first thing that he ever noted wrong was the passage of a jelly-like cylindrical clot from the bladder. This occurred in 1900. There has never been great pain of any kind, except when a clot was passed; no vomiting or other gastric disturbance, but slight and progressive loss of flesh.

Operation was attempted for the second time in December, 1904, when the tumor was removed through an anterior incision. The mass was lifted out without great difficulty (Fig. 12).

Pathologic Findings.—The pelvis of the kidney is all but obliterated by a soft, hemorrhagic, yellowish mass of tissue. The kidney is represented by a small

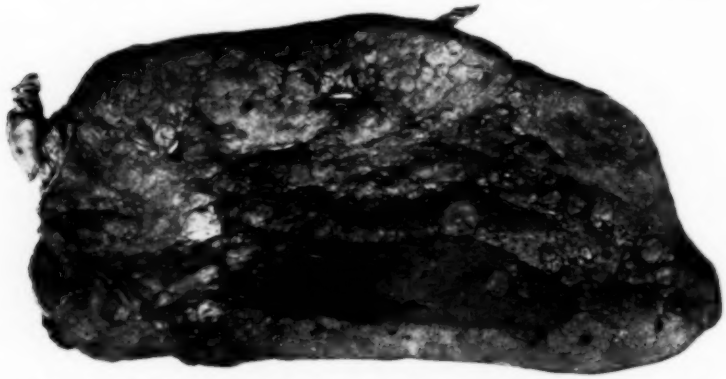

Fig. 18.—Photograph of a longitudinal section of the liver from Case 17, showing the multitude of metastatic nodules of tumor. Close examination of the liver shows a large number of tumor polypi projecting into the lumina of the veins.

fragment at the lower pole. The kidney structures are greatly reduced by a typical interstitial induration.

Microscopic examination of the tumor shows the tissue to be made up of a congeries of irregular spaces, with walls on which are tunics of clear cells arranged in irregular layers and of good size and intense staining properties. The cell cytoplasm is invisible. The cavities so lined are filled with a homogeneous pink staining material, that resembles closely the colloid matter in a goitrous thyroid, in fact, there are areas that puzzle one for a time to differentiate from goiter. Since recording this case I have received the information that this patient was attacked with jaundice and died within two weeks of the time of taking to bed. The emaciation was very rapid, the liver greatly enlarged and the jaundice very deep. Postmortem was forbidden. It is very fair to presume that the patient died of hepatic metastasis of the hypernephroma. Death occurred July 20, 1907, three years of good health intervening between the operation and death.

CASE 16.—*History.*—Cow, 4 years old, slaughtered at the Kansas City branch of Armour's. Large tumor of the right kidney. Clinical history not obtainable.

Pathologic Findings.—The tumor measures eighteen inches in length and nine inches in diameter. A small fragment of the kidney is attached to the lower pole of the kidney. Cross sections of the growth were submitted to me by Dr. Kinsley of the Kansas City Veterinary College for diagnosis. The growth is soft in consistence and of a sulphur yellow color, save in areas occupied by hemorrhagic extravasations. The tumor is divided into circular areas by white fibrous tissue.

Microscopic examination shows a very richly cellular mass. The cells are

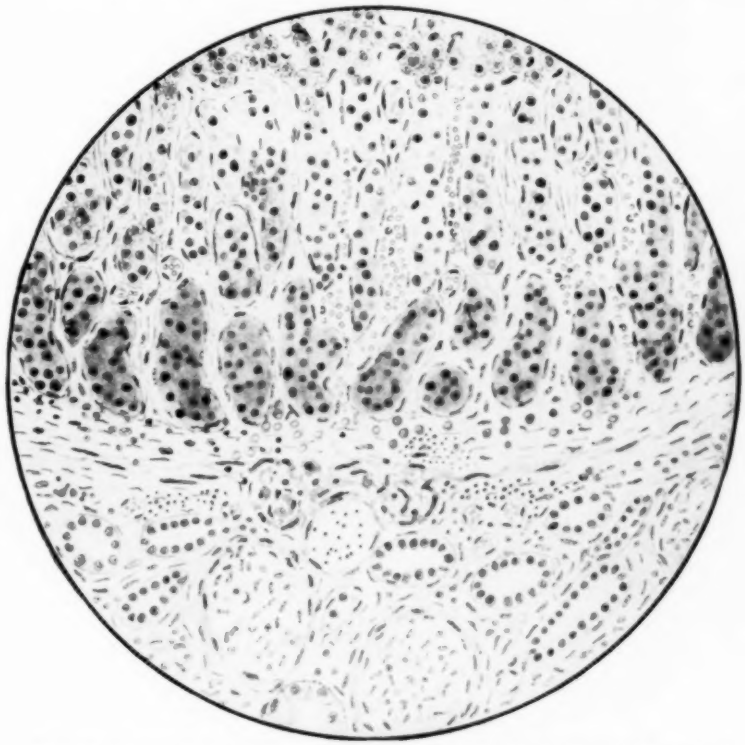

Fig. 19.—Shows a typical misplaced, non-neoplastic adrenal beneath the capsule of the kidney. Drawn from specimen 71.62-6, University of Chicago.

for the most part indefinitely outlined and present a very large oval, or spherical, deeply staining nucleus. The cytoplasm is granular and slightly basophilic. None of the clear vesicular type of cell is seen that is so common in the human hypernephroma. In a few areas of the tumor there are cysts filled with a pink staining, slightly granular substance, and lined with a single layer of the epithelial cells. In those regions, the impression is given that the tumor is a papillary cyst-adenoma. A gram of the tumor tissue ground up with 50 c.c. of water

yielded a milky fluid, two drops of which completely decolorized 25 c.c. of an iodin-starch mixture. This is the chemical test that Croftan has described.

This case is from the gross aspect a typical hypernephroma. The microscopic picture is typical so far as the arrangement goes, but the cells themselves are not

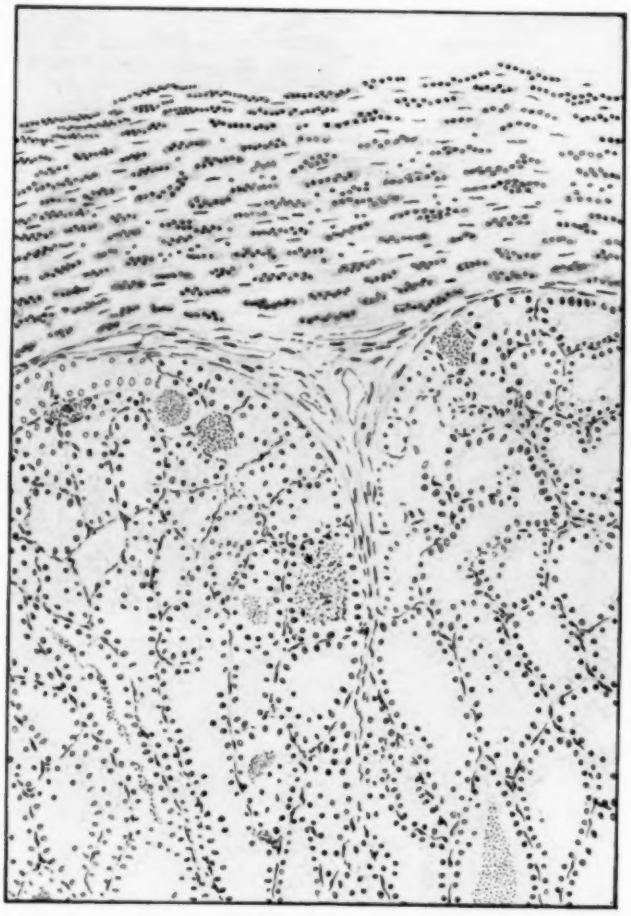

Fig. 20.—Cross section of a nodule from beneath the capsule of a kidney, the seat of a hypernephroma. The specimen shows a rind of typical adrenal tissue with a center of typical hypernephroma of the simplest type. Specimen in museum of the Northwestern University, Chicago.

like those generally found in the human tumor. I have, nevertheless, no hesitancy in reporting the case as one of hypernephroma. The inspector who examined the carcass of the cow reports that the renal vein looked like a large

sausage, from the kidney to very near the vena cava. There were no metastases noted in any of the important viscera.

CASE 17.—*History.*—Mrs. F., aged 56; married; chronic enlargement of the liver, probably fatty or amyloid. Married at the age of 21. Has had six children, five of whom are alive and in good health. About five years after marriage, she had an attack of rheumatism that lasted several weeks. She enjoyed fine health after this until her thirty-eighth year, when menorrhagia began. Examination at this time showed a small fibroid of the uterus. The hemorrhages continued until after the menopause at 48. At about 45 years of age the patient had a very severe attack of pain in the left side that was diagnosticated

Section 21.—Section of a hypernephroma (Specimen 71.62-15, Rush Medical College) which shows the cell columns hollowed out by blood corpuscles. Such a picture has led to a diagnosis of hemangiosarcoma with hypertrophy of lining endothelium.

as splenitis, and hot applications were applied for at least two weeks. The pain gradually receded, but did not entirely disappear for months after. No urinary examinations were made at the time of the supposed attack of splenitis. There was no temperature during the illness. During this entire period, the patient suffered with great nervousness and fainting spells. The heart seemed to be the seat of some neurotic disturbance. In 1903, her health was so broken that a trip to Cuba and from there to New York was taken in the hope that a sea

voyage would be of benefit. The trip did no good, but on the contrary, seemed to make incursions into her energies more than her home duties.

Careful physical examination made in April, 1905, revealed a murmur over the entire heart area. The heart seemed to be of normal size. No definite lesion could be affirmed. Examination of the abdomen revealed a much enlarged liver that the patient stated was noted by her dressmaker several months before. The liver extends downward to three inches below the umbilicus, and to the left of the nipple line. It was thought that some nodules could be made out on the edge of the liver. The pulse was strong, full, and eighty to the minute. The temperature was normal. The patient was at this time fairly well nourished. Chemical examination of the urine showed no albumin or sugar. Early in the winter of 1905 the patient returned from a trip east, not benefited by the change.

I saw the patient at this time and after a consideration of the long history, the enlarged liver and the negative findings in the blood and urine, ventured a

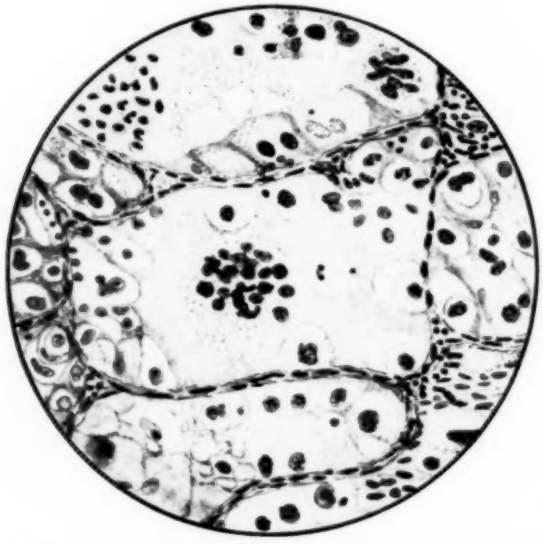

Fig. 22.—Cross section of a metastatic hypernephroma in the knee. (Specimen in Rush collection.) Shows the disposition of some examples to the formation of giant syncytial masses.

diagnosis of fatty or amyloid liver from unknown causes. At about this time *x*-ray treatment was instituted over the hepatic region. Marked shrinkage in the liver was effected by the treatment, the edge receding about two inches within the lines previously noted. At about this time, a pain appeared in the right hip and along the sciatic nerve. Nothing seemed to relieve this. The urine now contained a small amount of sugar, no albumin, no casts and no blood. During the last six months walking had been impossible on account of pain in the legs and weakness. In June of the present year there appeared an oval tumor in the center of the frontal bone. This was attended by intense frontal headache. Another similar tumor appeared on the parietal bone. These grew fairly rapidly until

death. A few days after the appearance of the parietal tumor great pain developed in the left shoulder and in the ribs. The latter was thought to be intercostal neuralgia. Temperature ranged from 98.6 to 106 F. during the last six weeks of her life. The high temperature existed for three days before death. Unconsciousness was profound for the last fifteen hours. This is one of the most remarkable case histories in the literature of hypernephroma. The postmortem report that follows shows the left kidney to be the seat of the primary growth. It is certain that the splenitis twelve years before was nothing less than a manifestation of the growth. The enlarged liver had existed for at least two and a half years.

Pathologic Findings.—Body emaciated, the skin yellowish and dry. The bones and joints show clearly through the skin. The abdomen is markedly enlarged on the right side from the crest of the ileum to the costal arch. The skin over this region is dappled brown from an *x*-ray burn. Rigor and lividity absent. The

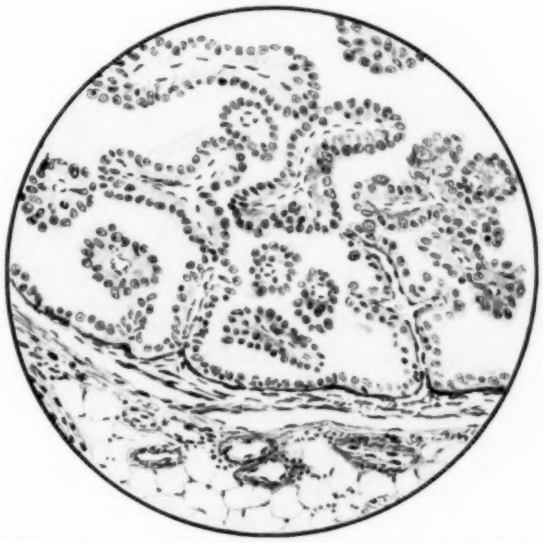

Fig. 23.—Section of hypernephroma (Rush No. 3.71.59 Cook County Hospital), showing a picture of papillary cyst-adenoma of kidney. Other fields from this tumor are typically that of the fascicular hypernephroma.

superficial blood vessels of the chest are very hard and tortuous, as from sclerosis. The vessels of the hands, forearms and legs are similarly diseased. On the forehead, above the outer angle of the right eye, is a soft, rounded tumor measuring 3.5 cm. in diameter and elevated 1.5 cm. above the skin level. This tumor seems to emerge from the bone. The color seems a deep yellow as it shows through the thinned and non-adherent skin. There is an exactly similar tumor over the left temporal bone. None of the superficial glands are enlarged. (At this juncture I felt that the frontal bone tumor, together with the long history, justified the diagnosis of hypernephroma and prophesied the finding of the primary tumor in the left kidney, as that was in line with the splenitis of years ago.)

The median section shows practically no subcutaneous fat. Intestines distended with gas. The liver extends 12 cm. below the ensiform cartilage in the median line. The left lobe extends to the spleen on the left, the right lobe extends to the crest of the ileum. The surface of the liver shows many bright yellow circular spots, of varying size and slightly elevated, but not umbilicated (Fig. 18). These areas of neoplasm are more abundant on the under surface and are here more elevated. The mesentery is free from fat. The abdominal blood-vessels are distended with blood. The mesenteric lymphnodes show no enlargement. All the tissues within the abdominal cavity are very dry. No fluid in the peritoneal cavity. The entire system of retroperitoneal lymphnodes is enlarged,

Fig. 24.—Hypernephroma of the broad cell-column type of fascicular zone origin. The regular alternation of cell-column and blood-vessel is seen (Case 11).

some to the size of walnuts (Fig. 17). The right ureter is distended with fluid. The right ovarian vein is markedly varicose. Left ovarian vein is slightly varicose. The left ureter is normal. The left kidney near its middle shows a yellow nodulated tumor mass projecting above its capsule. The mass is encircled at its lower margin by a very large blood vessel. The left adrenal is in place and is of normal aspect, but shows a good-sized blood vessel that runs direct from its lower pole to the upper aspect of the tumor mass, coursing for a short distance over its surface and penetrating it at its juncture with the kidney substance (Fig. 16).

On splitting the kidney, this vessel is again seen in about the center of the tumor mass, where it is filled with very bright yellow tumor tissue, contrasting strongly with the dull yellowish-red of the rest of the tumor tissue. Cross section of the adrenal shows no definite gross change.

The kidney tumor measures 6x4 cm. and is sharply circumscribed. There is a spherical nodule projecting free in the pelvis measuring 1.5 cm. This nodule is pure white in color. The main tumor mass is disposed in round areas, divided by white bands of connective tissue (Fig. 15). The individual areas differ much in color, being red, reddish-brown, yellowish-brown, light yellow and white. The consistence is uniformly firm. The topography is typically that of a hyper-

Fig. 25.—Shows the structure of a specimen of hypernephroma of the narrow tubular type. Such examples are usually described as adenomata of the kidney. In this case, the renal vein was involved by a cylinder of bright yellow tumor tissue of perfectly typical hypernephromatous tissue.

nephroma, the color hardly as yellow as most examples. The spleen is of a bluish color, normal in size and flaccid in consistence. There are no tumor deposits in this organ.

The right kidney is normal in size, shape and consistence. Cut section shows a pale yellowish-gray color and a slightly granular surface. The pelvis is slightly distended. The cortex is somewhat thin. The medullary pyramids are thickened

and each has a white granular tip. The capsule strips with difficulty. There are no deposits of adrenal tissue on the surface of this organ. The right adrenal is in place and is normal. The stomach is distended with gas. A careful examination of the stomach shows no tumor deposits or other definite pathologic condition. The pancreas is thoroughly involved in a mass of tumor nodules. The abdominal aorta from its point of emergence through the diaphragm to the bifurcation is tightly surrounded by masses of tumor. The lumen of this vessel is very much contracted from a most extreme degree of sclerosis. The entire inner surface is a succession of brittle calcareous plates (Fig. 17). The right ovary is small, hard, flat and pearly white. There is a small fibroid on its surface. The left ovary is like its fellow. The uterus shows a fibroid the size of a lemon on the right side. Section shows a very sclerotic uterine wall and several small submucous and mural fibroids.

Thorax: Lungs collapsed, dry and almost airless. The pleural cavities free from fluid. The heart is enormously enlarged, the rounded apex resting in the left axillary line. The pericardium is free from fluid. All the coronary vessels are greatly distended with black blood. The auricles are both distended with blood. The left ventricle is empty. The mitral valve is smooth and normal. The cut ends of the coronary arteries are as hard as flint, their lumina very much reduced. The walls of the left ventricle are somewhat thin, the musculature pale yellowish-brown and very flabby. The right ventricle contains a firm white clot intertwined about the cordæ tendinæ. The pulmonary artery contains a long dendritic white clot. The valve is normal. The tricuspid is normal. The aorta shows a considerable degree of uniformly distributed sclerosis. The valves are normal. The left lung is collapsed over most of its extent. There are no tumor nodules present. The cut surface is dry and bright brown in color.

The right lung is adherent at the base to the spinal column and diaphragm. On tearing it loose a spherical tumor nodule is found projecting from the visceral pleura that measures 1 cm. in diameter. Several other similar nodules are found on the parietal pleura at this point of adhesion. Their cut section shows a firm yellow tissue. The tumors are divided into areas by bands of fibrous tissue. A few small spots of hemorrhage are seen in most of the nodules. Fair-sized tumor masses are found in several of the ribs at their junction with the vertebræ. The peri-bronchial lymphnodes are free from tumor tissue. A tumor is noted in the fourth rib at the junction of the inner third. This all but produces a pathologic fracture. Another metastasis is in the second rib two inches from the base. It has completely severed the rib. The third rib is the seat of a pathologic fracture about three inches from the base. Examination of the tumors of the skull and search in the humeri is not permitted.

Microscopic Examination.—The tumor in the kidney presents, when the knife catches the tissue favorably, rough columns of very irregular cells. The columns are more or less widely separated by finely fibrillated connective tissue richly vascularized. When these columns are cut across, the cells appear in roughly outlined alveoli. The cells at all times are intimately associated with the surrounding connective tissue, and in many instances are separated from the blood vessels by a single layer of endothelium. There is not a trace of that disposition for the cells to rest by their ends on the capillaries, so usual in the ordinary hypernephroma. The cytoplasm is not clear, but is almost universally finely granular and strongly oxyphil. The size and shape of the cells is variable in the extreme, some areas are wide expanses of cytoplasm with many very large nuclear vesicles but no sign of cell walls. At other points even in the same column, the cells are about the size of a normal adrenal cell, polygonal, clearly defined, and possessing a single, well-stained vesicular nucleus with a large red nucleolus. At no place in the tissue is any pigment to be found in the cells, nor are there any

karyokinetic figures present. Many of the cells show at their periphery small circular vacuoles similar to those common in the cells of the adrenal. Cell inclusions form a marked feature in the cells of both the kidney neoplasm and the extensions in other organs. There are many places where the cells seem to have escaped from their usual columnar arrangement, and are seen as wide territories of polygonal cells with a good quantity of red blood cells between the tumor elements. (A case described by I. W. Blackburn as primary sarcoma of the adrenal in the *American Journal of the Medical Sciences*, 1906, p. 266, is a tumor of almost exactly the histologic characters of this case, except that his case presents the cellular pigmentation of the adrenal cells from the zona reticularis, while this shows no such pigment in the cells. All his figures, so far as the arrangement and cell morphology goes, could have been drawn from sections of this case.) Since the tumor is almost exactly similar in all the organs, no detailed description will be given, except as there appears something of particular interest.

In the liver, multitudes of smooth polypoid projections of tumor tissue into the lumina of the hepatic veins are noted in the gross specimen. On microscopic section these are found to be spherical aggregations of tumor cells that have destroyed the vessel wall and are growing into the lumen of the vessel, pushing only the endothelial lining ahead of them. At a few points, the endothelial investment is broken and liberated cells are found mingling with the blood in the vessel. In several of the larger hepatic deposits central softening has occurred, and amid the degenerating tumor tissue are multitudes of acicular clefts remaining from the solution of cholesterin crystals.

The left adrenal presents some peculiar features that are well worth noting. In the gross, the gland shows over its surface a dozen or so small rounded elevations like yellow miliary tubercles. On section these are found to project almost through the cortex of the gland. Their color is very much more yellow than the surrounding cortical tissue. Microscopically, these bodies are found to be composed of broad columns of cortical cells that present intensely oxyphil cytoplasm and a very dark dense nucleus. The columns are brought to a focus at the medullary portion of the gland and the whole nodule seems to be rather sharply circumscribed from the rest of the normal adrenal cortex. The columns of cells as they sweep up toward the capsule from their common point of origin remind one of a cross section of a huge taste bud, the individual sustentacular cells of the latter being represented by columns of cortical cells. Very likely this structure is an adenomatous condition that is comparable to the change in the thyroid in adenomatous goiter. The remainder of the adrenal seems to be fairly within the range of the normal. The zona reticularis seems to be broadened considerably and the cells of the zona glomerulosa are the seat of an unusual amount of fat.

In concluding this paper, it might be of interest to present some figures drawn from sections of various examples of undoubted hypernephromata that would represent tissue pictures not usually illustrated by writers on this tumor. For more typical figures the student is referred to papers indicated in the bibliography. It is from the presentation of a variety of tissue pictures that the true conception of the histology is to be obtained. The sections from which these figures are drawn were for the most part secured from the material contained in the museum of the Rush Medical College of Chicago.

Figure 23 is a fair example of the appearance of the normal misplaced adrenal tissue beneath the capsule of the kidney. This case is one

numbered 71.62 -6 University of Chicago. The finding is an accidental one in the course of a routine postmortem. I have an identical specimen (Fig. 14) of the photographs of gross specimens. These ectopic adrenals are not so common as the literature would lead one to believe, as inquiry among a number of pathologists with large postmortem experience elicits but few affirmative answers. I have encountered but the single example in over two thousand postmortems. Careful search has always been made for implantations elsewhere than on the kidney, but without success. In the case of an infant, recently autopsied at the University of Michigan, I was shown sections of small spherical nodules of adrenal tissue that were said to cover the peritoneum and connective tissue in the entire region of one of the adrenals.

In searching for material that would surely indicate the origin of the malignant hypernephroma from such a rest, but one specimen was found that could be so interpreted, and that specimen is in the museum of the Northwestern University in Chicago (Fig. 20). The gross specimen shows on the upper pole of the kidney an oval yellow mass, as large as the normal adrenal, enclosed in the kidney capsule. The nodule is smooth, and alone, would be taken for a large, but non-neoplastic, ectopic adrenal. The kidney itself is almost replaced by a typical hypernephroma. The section shows a thin rind of typical adrenal cortex enclosing a sharply demarcated spherical mass of typically hypernephromatous tumor tissue. The specimen looks as if the tumor had begun in the center of a normal adrenal gland. Nothing is said in the notes about the presence of the adrenal in the normal position, so it is uncertain as to the existence of the normally placed gland.

Figure 21 shows an example of a very hemorrhagic tumor, in which the blood had entered some of the softened cell columns and seemed to be using the new channel as a blood vessel. Such tumors have been mistaken for hemangiomas with cubical endothelial cells lining their walls. In many examples of the tumor small areas may be found presenting this confusing feature.

Figure 22 presents a cross section of the cell columns of tumor, metastatic in the knee of a boy. The center of the columns is seen filled with a syncytial mass of protoplasm containing many nuclei. Such a tumor is not infrequently identified as a giant-celled alveolar sarcoma.

Figure 23 shows a very common formation that can be found in many examples of the growth, if some of the outlying nodules be examined. Here the cells farthest from the supply of blood in the fine capillary supporting the cell column undergo a serous degeneration,

leaving a finger of cells floating free in a cystic cavity. Such tissue pictures lead to an erroneous diagnosis of papillary cyst-adenoma.

Figure 24 shows the broad cell-column type of fascicular hypernephroma. Here nutrition is perfect and we have a picture of a richly vascularized carcinoma, or of perithelioma. The bright yellow color in the gross specimen makes its nature apparent.

Figure 25 shows a fine example of the narrow cell-columned type in which a few of the columns are hollowed out, presenting the picture of a tubular adenoma.

In some of the examples of the tumor, cell arrangement is so lost that a histologic diagnosis is all but impossible. Such tumors are called sarcomata, and only the yellow color in the gross, and the chemical reactions, serve to identify them.

CONCLUSIONS.

We have here a tumor whose character is most variable as to details of histologic structure; yet, all in all, these several varieties can hardly be mistaken for anything else. They all, whatever their particular and individual vagaries may be, have a distinctive chemistry; they all contain a high proportion of cholesterin, lecithin and fat. The power of a watery extract of hypernephromatous tissue to reduce the color of a starch-iodin solution is very striking—the change being produced in a few seconds, or at most minutes, by a few drops of the extract, makes the test applicable in the operating room. In the case of other tumors, no example of carcinoma or of sarcoma produced this reduction of color in thirty-five cases tried by me.

More constant than the histologic structure, is the yellow color of the fresh gross specimen, and the great tendency of the neoplasm to hemorrhage, necrosis, hyaline degeneration of the stroma, and fat infiltration. The invasion of the renal vein is almost pathognomonic of the tumor.

Clinically, the tumor is found at all ages. The very young patients who can reasonably be supposed to be born with the tumor show a strong disposition to some peculiar metabolic changes, such as obesity, hirsuties and abnormal development of the sexual system. The vast majority of the cases present the clinical evidences of the growth in later middle life. Hematuria of an intermittent type, increasing in severity, seems to be the usual rule. Such cases, in the absence of palpable tumor, are commonly regarded as cases of renal stone, as cachexia is seldom a marked feature.

Prognosis based on the microscopic structure is absolutely unreliable, as the tumor of most malignant aspect may not have produced metastases;

and, on the other hand, a very small, quiescent and innocent appearing renal deposit may scatter its secondary tumors widely in the body.

With all these features before me, it seems justifiable to regard the tumor as a true and peculiar species, well worthy of a place of its own, to be studied and treated as a wonderfully individualized tumor type that lends itself poorly to any scheme of classification that contemplates the association of it with carcinoma or sarcoma. Hypernephroma is without doubt the most common of primary renal neoplasms.

422 Argyle Building.

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PAROXYSMAL HEMOGLOBINURIA.*

ACCOUNT OF TWO CASES.

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The first of the two patients, A, who furnish the basis of this report is a man 29 years old, who was born in Hungary, and served as a soldier in that country. During his military service he suffered much from chilblains during the winter, but he never had an attack of hemoglobinuria until December, 1902, eight months after coming to America.

During the summer of 1902 he lived in Saginaw, Mich., where he suffered much from mosquito bites.

There is absolutely no history of any infection or illness until December, 1902, when the patient first observed the attacks of hemoglobinuria, which were invariably associated with exposure to cold. We had no opportunity to observe any chilblains in this patient, but he says that when his feet or hands are thoroughly chilled they become very white, then blue and finally red, swollen and feverish. The swelling lasts several hours. According to the patient's account of himself, such an attack is always followed by a "black-water" attack.

Besides the chilblains there is nothing unusual in the history of paroxysmal hemoglobinuria of this patient. We found that attacks could be produced by exposure to cold. If the patient placed both hands in ice cold water for five minutes no hemoglobinuria followed. Sitting before an open window for fifteen minutes, clad in hospital garb, when the out-door temperature was about 10 degrees C., was followed by a characteristic chill, fever and hemoglobinuria. If one foot was placed in a pail of water, 8 degrees C., for thirty minutes an attack would follow. During the interim the patient's blood showed a coagulation time of three and one-half minutes. Directly after an attack, while the temperature was still elevated, the coagulation time was the same.

On March 3, 1908, the patient's blood-count was the following:

W. B. C., 7,800.	R. B. C., 4,520,000.
Hb. (Sahli), 92.	Tallquist, 85.

*Read in the Section on Practice of Medicine of the American Medical Association at the Fifty-ninth Annual Session, held at Chicago, June, 1908.

A differential count of 200 white cells gave the following results:

Polymorphonuclear cells,	158 =	79 per cent.
Small lymphocytes,	31 =	15.5 per cent.
Large lymphocytes,	8 =	4 per cent.
Eosinophiles,	3 =	1.5 per cent.

Repeated search for blood parasites proved negative, as did also all attempts to cultivate any organisms from the blood by the usual methods employed for such purposes. These examinations were made during the attacks and during the interims. On March 13 an attack was produced by placing the patient's foot in a pail of water at 8 degrees C. The following observations were made before, during and after the induced attack of hemoglobinuria.

The patient's foot was placed in the water at 10:50 a. m. Although there were some subjective premonitory signs of a chill at 11:50 it was not until 11:55 that the rigor was pronounced.

The temperature by mouth was:

At 10:20 a. m., 98.3 degrees.

At 11:20 a. m., 97.6 degrees. Subjective symptoms of muscular soreness.

At 11:50 a. m., 97.4 degrees. Chill apparent.

At 12:24 p. m., 100.2 degrees. Patient felt warm; urine passed rich in hemoglobin.

At 12:45 p. m., 102 degrees.

At 1:20 p. m., 100.2 degrees.

The arterial blood pressure was 146 mm. Hg., systolic pressure, before, during and after the attack.

The diastolic arterial pressure during the corresponding periods was 95. The chill and fever did not, therefore, modify the systolic or the diastolic blood pressure.

During the febrile period at 12:50 p. m. blood drawn into a syringe containing a small amount (2 per cent. of a 1 per cent. solution) of potassium oxalate and immediately centrifuged showed a distinctly pink serum which gave only the absorption bands of oxyhemoglobin to spectroscopic examination. Blood drawn and treated in the same manner before the patient's foot was placed in the cold bath revealed a normal serum. A few days later a cantharides plaster was applied to the arm. Three hours later when the serum was expected to accumulate in the underlying blister an attack of hemoglobinuria was induced. This serum was pink and showed the oxyhemoglobin bands under the spectroscope. A cantharides blister during an interim showed straw-colored serum.

The leucocyte count before an induced attack was 6,000; at the end of the chilly period the leucocyte count was 17,000 and was due to an increase of the polymorphonuclear cells. The leucocyte count made on March 7 was as follows:

At 9:00 a. m., before the chill,	= 6,000
At 11:30 a. m., after the chill,	= 17,000
At 1:00 p. m.,	= 15,000
At 4:00 p. m.,	= 11,000

During this attack the red cells were reduced 700,000 per c. mm. An ophthalmoscopic examination during one of the attacks revealed nothing abnormal in the eye-ground.

During the attacks the urine was colored a dark chocolate hue and showed nothing more than the presence of albumin, hemoglobin and casts of blood pigment.

From the above observations it was apparent that exposure to cold caused hemoglobinemia which was well pronounced before the febrile period. It is also clear that the rigor is associated with a slight lowering of the body temperature, and that the rise in temperature marks the cessation of the chill, which is unlike the relations between rigor, temperature and sense of warmth in the course of infectious diseases with which we are familiar.

The rise in temperature is associated with a pronounced polymorphonuclear leucocytosis.

The second patient B, an American, 25 years old, was admitted to Lakeside Hospital April 18, 1908. This patient was much more sensitive to cold than patient A. Without any history of illness or infection of any kind which could have any bearing on his present illness, B commenced having paroxysmal attacks of hemoglobinuria identical in character with those of A, eighteen months before admission to the hospital. As in A, the physical examination revealed absolutely nothing of an abnormal character. During warm weather he is perfectly comfortable, but if the thermometer is as low as 10 C., he is liable to an attack. He is particularly sensitive to a cold, moist wind, and has had as many as three attacks in one day. This patient gave no history of chilblains as did A, but at the conclusion of an attack there would be on the trunk and arms several small macules about one-sixteenth of an inch in diameter, in the middle of which a small blister would rise, from which the serum would escape during the febrile period and leave a very minute particle of desquamating epithelium apparent in the middle of the red

areola. By the following morning all traces of the skin manifestations were gone.

The observations made on patient A were repeated on patient B. B suffered from a malady identical in character with that of A; the only essential difference being one of degree.

STUDY OF THE SERUM IN THESE CASES.

We then undertook a study of the serum of these patients from the standpoint of the side-chain theory, with the following results:

Although we were unable to find any organism in the patient's blood, either during the attacks or in the interims, it was clearly apparent that cold was essential for the hemolytic activation of the patient's blood.

Our first experiments consisted in attempting to activate the serum of these patients by exposing it to a low temperature, then warming the serum to 37 degrees C., and adding washed red-blood cells obtained from other patients with normal blood. After repeated trials with serum of these hemoglobinuric patients obtained by venous puncture and from blister serum (all of which were unsuccessful as long as the red cells were added to the serum when warm), we then chilled the serum after red cells had been added. When this precaution was taken, and the mixture warmed, hemolysis was complete within a very brief period.

All the experiments gave the same results with sera A and B.

Hemoglobinemic serum chilled in a salt and ice mixture at 5 degrees C., for thirty minutes, then put in an oven at 37 degrees C. for one hour, and after the serum again attained body temperature the red cells from a normal blood which had been repeatedly washed in physiologic salt solution were added to the serum and again put in the oven. The result was negative. The experiment and results are expressed in the following formula:

H. S. + 5° C. for 30 minutes + 37° for 1 hour + R. B. C. = 0.

In the next experiment the red cells were added before the mixture was exposed to a low temperature, and as soon as the mixture was again warmed complete hemolysis occurred. This was apparent by the disappearance of all cloudiness and the mixture becoming a clear ruby-red solution with a marked diminution of the viscosity of the serum.

H. S. + R. B. C. + 5° for 30 minutes + 37° C. for 10 minutes = +.

The serum from patient B, with added red cells, was placed in the ice water for fifteen seconds, then put in a water bath heated to 56 degrees C. for ten seconds, at the end of which time hemolysis was complete.

The serum from patient A required a longer exposure to cold to produce hemolysis, which is quite consistent with the comparative clinical histories of the two men. B was much more sensitive to cold than A.

Accidentally we discovered that if the suspension of red cells in the serum of B was placed near a 32-candle-power incandescent electric lamp after having been exposed to cold, hemolysis occurred very promptly.

If a suspension of red cells in the serum was placed in a water bath at 15 degrees C. for five minutes and then exposed to the rays of the lamp, which registered 25 C. on a thermometer placed beside the test-tube, hemolysis was prompt and complete, that is, it occurred at the end of eight minutes.

A drop of the suspension of red cells in serum from B was placed under the microscope after the mixture had been exposed to cold. The rays of an Abbé condenser supplied sufficient heat to cause rapid hemolysis, which could be observed under the microscope. Many cells disintegrated by fragmentation and many faded from view as the hemoglobin content was dissolved out of the stroma. The entire field was then filled with fragments of red cells which would certainly have been mistaken for blood platelets so far as their morphology was concerned.

If the suspension of red cells in serum A or serum B were exposed to a low temperature for hours, no hemolysis occurred until the mixture was again warmed.

The reduction in temperature necessary in the laboratory tests to procure activation of this lytic serum gives a very striking suggestion of the radiation of heat from the surface of the body and the subsequent warming of the blood from the surface, as it again meets the visceral blood, and it also illustrates the maintenance of the internal heat by metabolism.

If serum from normal blood was substituted for the lytic serum, and washed red cells from either A or B were substituted for the normal red cells employed in the former experiments, hemolysis did not occur.

This showed that the lytic principle was contained in the serum, and that hemolysis did not result from a diminished resistance of the patient's red blood cells.

If to a suspension of washed red cells (5 per cent.) in 0.5 c.c. normal serum, 0.03 c.c. of serum B was added it was found to be the minimum proportion of lytic serum necessary to cause hemolysis. So it may be said that approximately 6 per cent. of serum B added to normal serum was required to cause hemolysis of 5 per cent. suspension of red cells.

Thus far it is evident that cold (15 degrees C.) is essential for fixation of the lytic principle to the red cells, and that a temperature of 25 C. is necessary for the accomplishment of hemolysis.

This behavior of the lytic principle strongly suggests the applicability of the side-chain theory to this instance of hemoglobinuria.

In an article by Donath and Landsteiner[1] we find they had the same experience as we had in producing hemolysis *in vitro* with the serum from a case of paroxysmal hemoglobinuria, and, although they attempted to prove the applicability of various steps in the side-chain theory, they failed to reactivate the serum after it had been inactivated by heat at 56 degrees C. for ten minutes.

If the serum is heated to 56 C. for twenty-five minutes all attempts to procure hemolysis by exposure to cold and then to 37 C. are futile. This shows, of course, that there is an unstable substance essential for hemolysis which answers to the complement of Ehrlich's theory. It now remains to be shown that there exists also a stable substance which serves as the amboceptor between the complement and the red cells. The first step to prove this point requires a successful reactivation of the serum. If done by the usual method employed in hemolytic experiments as tried by Donath and Landsteiner the result is negative.

0.5 c.c. of inactivated H. S. + washed R. B. C. + 5° C. for 30 minutes + 37° C. for one hour.

Now if the normal serum be added and the mixture is placed in the thermostat for many hours no hemolysis follows.

Inasmuch as a low temperature was required to procure fixation of the amboceptor to the red cell it seemed probable that reactivation experiments had hitherto failed because a low temperature was not employed in fixing the complementophilic end of the amboceptor to the haptophore of the complement. The following reactivation experiment proved successful.

0.5 c.c. of inactivated H. S. + washed R. B. C. + 0.25 c.c. of normal serum + 5° C. for 15 minutes.

The mixture was then warmed to 37 degrees C. and hemolysis followed immediately.

Thus it is apparent that cold is essential for the fixation of both the cytophilic and the complementophilic ends of the amboceptor.

The foregoing experiments prove the existence of two essential factors in the lytic principle of the serum, one of which is unstable and is rendered inactive by heat and is present in all human sera; the other factor is more resistant to heat and is present only in the serum of patients in whom exposure to low temperature produces hemoglobinemia.

Eason[2] in his experiments on the serum of a patient with paroxysmal

1. Donath and Lundsteiner: München. med. Wchnschr., 1904, li, 1590.
2. Eason: Jour. Path. and Bacteriol., 1906-7, xi, 169.

hemoglobinuria by a different procedure showed practically the same point, although he failed to recognize the need of a low temperature to secure union between the complement and amboceptor. In his experiment red blood cells were added to the patient's inactivated serum and the mixture exposed to ice-water for half an hour. After the mixture was removed from the ice-water bath the complement from normal serum was added, how long after he does not state, but from our results the mixture must have been cold when the complement was added or hemolysis would not have occurred when the whole mixture was put in the brood oven.

If we are permitted to use the terms amboceptor and complement as applied to these two factors contained in the lytic serum it is incumbent on us to show that the union between the amboceptor and red cell is a biochemic union and one that can not be destroyed by washing the cells with physiologic salt solution after red cells have been exposed to cold in the presence of the inactivated serum from patients A and B respectively. At this period in our work we found that the oxalate serum did not differ from the serum which was procured by letting the serum separate out of the blood on standing. And as the serum could be procured more promptly and in larger amounts by centrifuging the oxalate blood, hereafter when the term H. S. is employed we shall mean hemoglobinemic serum to which 2 per cent. of 1 per cent. solution of potassium oxalate has been added.

The following is an experiment to show the fixation of the amboceptor which proved negative because the mixture was not exposed to a low temperature after the complement from a normal serum was added.

0.5 c.c. of inactivated H. S. + washed R. B. C. + 5° C.
for 1 hour.

The mixture was centrifuged and the supernatant fluid drawn off; the red cells were washed three times with large amounts of an isotonic salt solution. We then had presumably the red cells with the amboceptor fixed to them and clear of any of the excess of amboceptor which might have clung to the cells from the inactivated H. S.

If normal serum was now added to these (red cells + amboceptor), and the mixture placed in an oven at 37 degrees C. no hemolysis followed. In subsequent experiments, however, the mixture of (red cells + amboceptor) + normal serum was exposed to a temperature of 5 degrees C. for fifteen minutes and then hemolysis occurred as soon as the mixture was again warmed to 37 degrees C. Here again we have proof of the need of cold to procure fixation of the complementophilic end of the amboceptor to the haptophore of a normal serum.

The following experiments were made to show how the amboceptor could be exhausted from the lytic serum.

To 1 c.c. of inactivated H. S., five drops of a 10 per cent. suspension of washed red cells were added. The mixture was exposed to 5 degrees C. for one hour, then centrifuged and the supernatant serum drawn off. To the supernatant serum, red cells were again added and then 0.25 c.c. of normal serum added to the mixture. This mixture was exposed to cold for fifteen minutes and warmed to 37 degrees C. Hemolysis followed immediately, but it was not so pronounced as in our other reactivation experiments.

If to 1 c.c. of inactivated H. S. five drops of a 10 per cent. suspension of red cells were added, the mixture exposed to 5 degrees C. for one hour and then centrifuged, the supernatant serum again exposed to 5 degrees C. for one hour with five drops of a 10 per cent. suspension of red cells again added to the serum, and then centrifuged, the supernatant serum could not be reactivated.

Thus we have shown that if in two stages, ten drops of a 10 per cent. suspension of red cells be added to (1 c.c.) the serum and exposed to cold for one hour each time, the amboceptor can be exhausted from the inactivated hemoglobinemic serum.

From a number of such experiments we learned that if the serum with red cells was exposed to cold less than one hour we could not procure fixation of the amboceptor.[3] Thus far we have shown that the hemoglobinemic serum contains two factors, one unstable and capable of being inactivated by exposure to a temperature of 56 degrees C. for twenty-five minutes and is a factor which is common to all human sera and answers to the complement of Ehrlich.

The other factor is found only in the hemoglobinemic sera and is resistant to 56 degrees C. for twenty-five minutes. This factor answers to the amboceptor of Ehrlich and can be fixed in a biochemic union to the red cells and can be exhausted from the hemoglobinemic sera if a sufficient number of red cells be suspended in the serum and the mixture exposed to a low temperature for one hour.

In watching hemolysis take place under the microscope and seeing the extreme rapidity with which hemolysis occurred in the test-tubes we were impressed with the striking similarity between this hemolysis and the hemolysis which occurs when small amounts of ether are added to a test-tube of isotonic salt solution with red cells in suspension.

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3. Eason (Jour. Path. and Bacteriol., 1906-7, xi, 169) was able to procure fixation of the amboceptor after one-half hour exposure to cold. He was also able to exhaust the amboceptor by one-half hour exposure to cold.

The natural deduction from such observations was that the lytic principle of the serum attacked the lecithin, cholesterin or some other lipoid of the red-cell stroma. If this were the case, then an excess of a mixture of lecithin and cholesterin in the serum would satisfy the avidity of this lytic substance and protect the red cells from destruction.

The following experiment was made to show this point:

An emulsion of lecithin (Merck) in normal salt solution and a mixture of cholesterin (Merck) in normal salt solution were made. Both mixtures were very thick. Three drops of each were added to 0.5 c.c. of H. S. and the mixture permitted to stand for one hour. Washed erythrocytes were added to the mixture and the whole mass exposed to 5 degrees C. for thirty minutes and then put in the oven at 37 degrees C. for twelve hours. No hemolysis followed.

We found then in trying lecithin and cholesterin separately that lecithin did not in the least inhibit hemolysis, but that cholesterin always prevented hemolysis even in the slightest degree when present to the extent of 5 per cent. or more.

It remained to be shown how cholesterin exercised this inhibitory effect on hemolysis—whether cholesterin exercised merely a negative reactive influence or formed a union with the complement or with the amboceptor.

To the hemolytic serum an emulsion of cholesterin in normal salt solution was added, and the mixture permitted to stand in the oven at 37 degrees C. for one hour. The mixture was then centrifuged and the clear supernatant serum removed. To this clear serum cells were added and the suspension of cells in the serum put in the cold bath at 5 degrees C. for one hour. The mixture was then put in the oven at 37 degrees C. and at the end of twelve hours there was no hemolysis.

From this experiment we are permitted to assume there was a deflection of either the amboceptor or the complement. Unlike the behavior of the receptors of the red cells and the amboceptor, however, we found by repeated experiments that a low temperature was not favorable to anchorage of the cholesterin.

Cholesterin protected the red cells when 5 degrees C., 22 degrees C. and 37 degrees C. were employed, but the best protection seemed to be afforded when the cholesterin was in contact with the serum at 37 degrees C., so the affinity between the lytic principle of the serum and cholesterin was not identical in character with the linking of the amboceptor to the red cells.

The following experiments were then made to show whether the amboceptor or the complement was deflected:

One c.c. of the serum was inactivated by heating it at 56 degrees C. for twenty-five minutes. To this inactivated serum cholesterin in excess was added and the mixture permitted to stand at 37 degrees C. for one hour. The mixture was then centrifuged and the supernatant serum was clearer than the original unheated serum. We then assumed if cholesterin was fixed in this inactivated serum it must be fixed to the amboceptor.

To this clear serum washed erythrocytes were added and the suspension was exposed to 5 degrees C. for one hour. The mixture was then warmed to 37 degrees C. and 0.4 c.c. of normal serum was added and the mixture again chilled at 5 degrees C. for one hour. The mixture was then put in the oven at 37 degrees C. and in thirty minutes hemolysis was complete.

Therefore, treating the inactivated serum with cholesterin did not prevent anchorage of the amboceptor to the red cells.

The following method was then employed to show whether cholesterin deflected the complement or not in a reactivation experiment:

One c.c. of H. S. was heated at 56 degrees C. for twenty-five minutes. Red cells were then added and the mixture chilled at 5 degrees C. for one hour to fix the amboceptor. Cholesterin was then added to the mixture after it stood in the oven at 37 degrees C. for twenty minutes. Normal serum was then added to the mixture which was chilled at 5 degrees C. for thirty minutes. The mixture was then warmed and permitted to stand until the following day, but there was no hemolysis. This experiment shows that cholesterin acts by deflecting the complement.

Early in our experiments on these patients we tried calcium lactate as a remedy against hemolysis in both patients. They were given sixty grains a day over a period of two weeks, but at the end of that period the patients responded to cold as before and the hemolysis *in vitro* was unaffected. Nor did calcium lactate inhibit the hemolysis *in vitro*. After our experiences with cholesterin in the laboratory we administered cholesterin to these patients per os ten grains three times daily dissolved in olive oil. After ten days' trial of the cholesterin treatment we found that hemolysis *in vitro* was unaffected in both patients. The weather during this period was very warm, so neither patient had an attack, and although neither patient objected to repeated venous punctures for obtaining blood, they did not wish to expose themselves to an attack of hemoglobinuria by exposure to a cold foot bath. So whether the cholesterin therapy may offer protection against attacks due to exposure to cold or not remains undecided.

We make this statement in view of the experience which Widal and Rostain[4] had with their patients, on whom they were able to confer passive immunity by means of an antihemolytic serum. Although the patients of Widal and Rostain enjoyed immunity from attacks on exposure to cold, their sera was as actively hemolytic *in vitro* during this period of immunity as before.

We repeated the experiment of Widal and Rostain in procuring an antihemolytic serum from a rabbit by treating the animal with normal human serum.[5]

The rabbit was given four intraperitoneal injections during a period of three weeks. The amounts of normal serum used at each injection were 5 c.c., 15 c.c., 12 c.c. and 12 c.c. respectively.

To inhibit the lytic action of these patients' sera on red cells we found it necessary to employ about 12 per cent. of the inactivated immune rabbit's serum added to the serum of patients A and B. Normal human serum was hemolytic to the rabbit's washed red cells, but the sera from our patients was more strongly hemolytic than normal human serum.

In tube A was placed 10 c.c. of normal human serum and in tube B was placed 10 c.c. of hemoglobinemic serum from patient B. To each, i. e., A and B, were added 1 c.c. washed red cells from the rabbit. Both tubes were chilled at 5 degrees C. for twenty minutes and then both tubes were put in water (55 degrees C.) for fifteen seconds. Both tubes showed hemolysis immediately, but the hemolysis in tube B was more complete than in tube A. We also found that normal human serum completely laked the rabbit's cells at 37 degrees C. in forty-five minutes without the previous exposure to cold.

The treated rabbit's serum also completely laked normal human red cells at 37 degrees C. in forty-five minutes without previous use of cold.

To test the antihemolytic property of this "sensitized" rabbit serum it was, of course, necessary to inactivate the serum at 56 degrees for twenty-five minutes.

We then found it was necessary to add as much as 12 per cent. of the inactivated rabbit's serum to the serum of patient B before hemolysis could be completely prevented. The antihemolytic property of our rabbit's serum was not so highly developed as in the rabbit of Widal and Rostain, probably because the rabbit was treated for a shorter time than was the rabbit in the hands of Widal and Rostain.

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4. Widal and Rostain: Compt. rend. Soc. de biol. de Paris, 1905, l, 321.

5. Eason (Jour. Path. and Bacteriol., 1906-7, xi, 203) employed the serum of a patient suffering from paroxysmal hemoglobinuria for the same purpose. Any human serum serves the same purpose.

Widal and Rostain found that they could confer a passive immunity on their patients by subcutaneous injection of 25 c.c. of the inactivated serum from the sensitized rabbit. This immunity against cold lasted for only ten days. But during the immune period the lytic property of their patients' serum *in vitro* was undiminished.

This antihemolytic serum of the sensitized rabbit inhibits the hemolysis if it is added to the mixture of red cells and lytic serum after exposure to cold.

The protection from this serum is by virtue of deflection of the complement and is not due to antiamboceptor.

The question of etiology arises in relation to these experiments in hemolysis in the following manner:

1. Is the lytic property of these patients' sera due to a want of the normal antihemolysin which is presumed to be present in the sera of all normal animals?

2. Does the lytic principle of these sera partake of the character of a catalytic agent or a ferment?

3. Or is the lytic substance a biologic product of some form of infection which thus far has defied our attempts at detection?

If the first hypothesis were tenable we should expect to find hemolysis inhibited by the addition of inactivated normal human serum. This, however, is not the case. If inactivated normal serum is added to the fresh lytic serum in equal amounts and the mixture permitted to stand, either at a low temperature or at 37 degrees C. for an hour before red cells are added, hemolysis results after the mixture is exposed to cold just as in the original experiment.

The second hypothesis is not tenable because the amboceptor can be readily exhausted from the inactivated lytic serum by the exercise of its function of fixation to the red cells. A catalytic agent would not be sacrificed in such measured quantities by the exercise of hemolysis.

The third hypothesis does not admit of disposal. It is true that these patients are in good health as long as they are not exposed to cold, and the fact that they have hemoglobinemic fever can not be regarded as the direct effect of some organism. The abundance of cell shadows which must exist in the plasma of these patients after hemolysis occurs is quite sufficient to account for their fever. But patients may have infections without an elevation of temperature, and that, too, when organisms can be cultivated from their venous blood.

We had a patient in our wards at Lakeside Hospital during the past year who was a good example of an afebrile infection.

A young man 20 years old presented all the clinical signs of Hanot's

type of hypertrophic biliary cirrhosis of the liver with splenic tumor and slight icterus. The patient remained three months in the ward and during that time a careful watch of his temperature never detected a rise above 99 degrees F. From the fluid gained by punctures of the spleen and the liver and from blood obtained from the vein of his arm we were able to cultivate a large motile bacillus with many characteristics of the common colon bacillus. It is true that the patient was ill, but he was not ill on account of his infection, but on account of his diseased liver and spleen. With such experiences in mind it does not require a great flight of imagination to conceive of an infection of some kind being the underlying cause of our patients' hemoglobinemia.

Now, if such were the case we should expect to find some evidences of an antibody in the blood of the patient who has had his disease five years and who is less sensitive to cold than the other patient who has had his disease only one and a half years.

With this idea in view, inactivated serum from patient A was added in equal amounts to the fresh serum of patient B and inactivated serum from patient B was added to the fresh serum from patient A in equal amounts. These mixtures were permitted to stand one hour before red cells were added, but hemolysis resulted after the usual procedure of exposing the mixtures to 5 degrees C. and 37 degrees C. as in our earlier experiments.

As the matter at present stands we are justified only in saying that the hemoglobinemia which follows exposure to cold is due to some biologic product in the plasma which in its behavior admits of the demonstration of every step in hemolysis as expounded by the side-chain theory of Ehrlich.

In conclusion it gives us great pleasure to express our gratitude to Dr. J. J. Macleod, professor of physiology in Western Reserve Medical School, for valuable suggestions and consultations during the progress of our work.

Rose Building.

ERRATUM.—An absurd typographical error occurred in the title of Dr. Herrick's paper in the October issue of the ARCHIVES (p. 291), where the word "cure" occurred instead of "case."—EDITOR.

A COMPARISON OF THE VON PIRQUET, CALMETTE AND MORO TUBERCULIN TESTS AND THEIR DIAGNOSTIC VALUE.*

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When we decided to investigate the relative and individual merits of the newer methods of diagnosing tuberculosis, the literature did not contain the almost innumerable reports upon these procedures that are current to-day. But we feel that this in no sense detracts from whatever merit this communication may have, since we are now enabled not only to report on the results of our own investigations, but also to point out their relationship to the work which has already been done, which may add something in the general consensus to the clearing up of this undeveloped question. The tests which we have applied have been:

1. The conjunctival test of Calmette and Wolf-Eisner in one hundred and fifty-eight cases.

2. The scarification test of von Pirquet in one hundred and fifty-nine cases (using both human and bovine tuberculin in twenty-four cases).

3. The ointment test of Moro in one hundred and fifty-four cases.

4. The subcutaneous test in eighty-five cases in confirmation of the others.

PREPARATION OF TUBERCULINS.

It has seemed to us very important to point out that all the tuberculins which we have used in carrying out these tests have been prepared in one laboratory by the same method, and in order to make our results of value in comparison with others, to express briefly the method of preparation of our various solutions.

PREPARATION OF TUBERCULIN ORIGINAL (T. O.) (KOCH'S OLD TUBERCULIN).

A culture of the human type of the tubercle bacillus was grown at incubator temperature on glycerin beef broth for a period of six to eight weeks, or until the culture had covered the entire surface of the media.

*From the William Pepper Clinical Laboratory, University of Pennsylvania. Read before the Association of American Physicians, Washington, D. C., May 13, 1908.

The flasks containing the culture were then placed in a steam sterilizer for three hours, after which they were removed and the contents, including the growth of the tubercle bacilli and the beef broth, poured into a common vessel. This material was then sterilized in streaming steam for another period of two hours, it being considered that this prolonged exposure of the organisms to the streaming steam had some value in extracting the intracellular product of the tubercle bacilli. The organisms were then removed, first by filtration through paper and afterward by double filtration through a Berkefeld filter of the fine flow. The filtrate, which contained the toxins which had been liberated during the growth of the organism, as well as those extracted during the period of sterilization, was then evaporated over a water bath to one-tenth its original volume. This evaporated tuberculin was again passed through a Berkefeld filter, placed in bottles and sterilized by the intermittent method.

For the bovine tests, the tuberculin was prepared in the same way, substituting the bovine for the human culture.

PREPARATION OF THE TUBERCULIN PRECIPITATE (T. P.) FOR THE CONJUNCTIVAL REACTION.

Two volumes of 95 per cent. alcohol were placed in a tall cylinder and to this was slowly added one volume of concentrated tuberculin original. As soon as the precipitate, which forms early, had settled to the bottom of the cylinder, the supernatant liquid was decanted and the precipitate collected on a hard filter with the aid of a suction pump. It was afterward washed with 70 per cent. alcohol until the filtrate ran clear. It was dried in vacuo over sulphuric acid until perfectly dry; then it was broken up in a mortar into fine powder. This powder was then dissolved in normal saline solution to whatever strength was desired.

PREPARATION OF THE TUBERCULIN OINTMENT.

Equal parts by weight of tuberculin original and anhydrous lanolin were mixed together as follows: The lanolin was heated in a mortar until liquid. The mortar was then placed in an ice pack and the tuberculin slowly added, stirring vigorously with the pestle until the entire mass had become solidified. In this manner an even distribution of the tuberculin throughout the lanolin was obtained.

For use in the conjunctival test, the tuberculin was put up in small sealed capillary glass tubes, after the well known form used for vaccine containers, each tube containing three drops of the strength solution desired. The purpose in having three drops in each tube is to enable the

operator to remove one drop to wash away the possible spicules of glass which might adhere to the tube, the second drop being instilled and the third remaining behind to prevent the forcing out of any spicules of glass which may have come from the other end of the tube.

The solutions used for the cutaneous test were put up in bulk, as was also the tuberculin ointment.

STRENGTH OF SOLUTIONS USED.

In the application of the eye test, we have used a 0.5 per cent. strength in the great majority of cases. Occasionally, in the application of a second test to the original control eye, we used 1 per cent. strength; in a small group of older children, we used a 0.75 per cent. solution, while in children under two years of age, we used a 0.3 per cent. solution. A 10 per cent. solution of tuberculin original was used in the scarification tests, both human and bovine, and a 50 per cent. strength in the ointment tests.

TECHNIC.

Eye.—The rubber bulb was slipped over the end and placed in the middle of the capillary tube, after which both ends of the tubes were wiped off with alcohol and the ends broken by the fingers covered with sterile cotton, after which the bulb was placed in its proper position. The history of the patients as to previous eye conditions having been ascertained, the eyes were inspected to eliminate inflammatory lesions, and notes recorded descriptive of the general appearance. The lower lid of one eye (the other serving as a control) was then drawn downward and one drop of the solution placed in the lower inner portion of the conjunctiva. The lid was held in this position until the solution was well diffused throughout the conjunctival sac.

Scarification.—After the thorough cleansing of the upper arm with soap and water, followed by alcohol, three-minute scarifications, just deep enough to produce slight redness without drawing blood, were made at distances of about 5 cm. from each other in the length of the arm. One drop of the 10 per cent. solution was then placed on each of the upper and lower areas, by means of a sterile dropper. To the middle scarification, which served as a control, nothing was applied in the earlier cases, while in the later groups, one drop of the same solution minus the tuberculin, was used. The solutions were then rubbed carefully into the scarifications for a few moments, after which the arm was exposed until the solutions had dried.

Ointment Test of Moro.—The directions of its originator were followed in its application. After carefully inspecting and recording the

appearance of the abdominal surface and without any preliminary treatment of the abdomen, there was applied, either to the epigastric region, or more frequently to the submammary region, about 15 grains of the ointment. With a rubber finger cot or rubber glove, the ointment was gently rubbed into a circular area of from 6 to 7 cm. diameter for forty-five seconds. Over another area on the abdomen the same lanolin as that used in the combined ointment was applied in the same manner to serve as a control. The surfaces were then exposed to the air for twenty minutes. The ointment was not removed and no protective dressing was applied.

As our purpose was to determine the degree of uniformity of the various reactions, we used practically the same dosage for all cases and the same technic in their application throughout our work. We believe, however, that much smaller doses will yield equally satisfactory results, and that variations in the method of applying the scarification and ointment tests may be used advantageously. We are convinced, from the use of these latter tests, in cases not included in this group, that a smaller scarification for the cutaneous test and a less prolonged exposure after the application of the tuberculin is advisable, and that the removal of the excess of the ointment at the end of twenty minutes will limit the reaction to a smaller area in that it will avoid the spreading of the ointment when the clothing is replaced.

THE REACTION.

The principle of the reaction resulting from the application of these tests is, of course, the same in all. When an individual develops tuberculosis there occurs a hypersensitiveness of his tissue cells to the poisons of the tubercle bacillus, a condition for which von Pirquet has suggested the term "Allergie" (allergistic reaction); that is, the altered reaction which the human organism shows to micro-organisms or substances with which it is already acquainted, a reaction, in other words, in an organism with an acquired immunity. When, therefore, the tuberculin solutions are brought into contact with the various portions of the body, these reactions manifest themselves by the phenomena about to be described.

When a drop of tuberculin solution is instilled into the eye of an immunized individual, in from four to twenty-four hours there occurs an injection of the palpebral conjunctiva, semilunar fold, caruncle and orbital conjunctiva, which varies in intensity in different individuals, is usually attended by lachrymation and moderate fibrinous or fibro-purulent exudation, which may go on to profuse suppuration, attended by very marked swelling of the external, as well as of the internal tissues

Fig. 1.—Reaction to the conjunctival test—severe (+ + +). Note swelling and redness of the lids and cheeks, swelling of the caruncle, lachrymation and narrowing of the palpebral fissure. Control. (Sketch of single eye is from the same case.)

Fig. 2.—Reaction to the conjunctival test—severe (+ + +). Lower lid retracted. Note swelling and redness of palpebral conjunctiva, plica semilunaris and caruncle and intense injection with swelling of orbital conjunctiva.

Fig. 3.—Reaction to the conjunctival test—moderate (average) reaction (+ +). Lower lid retracted; eyeball turned outward and upward. Note swelling and redness of palpebral conjunctiva, plica semilunaris and caruncle, moderate injection of orbital conjunctiva. Control.

Fig. 4.—Cutaneous reaction—severe (+++).

Fig. 5.—Cutaneous reaction—moderate (++).

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Fig. 6.—Reaction to the ointment test—severe (+ + + +). (The unoccupied circle marks the control area.)

Fig. 7.—Reaction to the ointment test—moderate (++). (The unoccupied circle marks the control area.)

Fig. 8.—Reaction to the ointment test—very mild (+). (The unoccupied circle marks the control area.)

Fig. 9.—Return phenomena in the area of the ointment test following the subcutaneous injection of 0.00075 gm. of tuberculin. They occupy all of the areas with which the ointment came in contact, some of which did not show reaction to the primary test.

of the eye (Figs. 1, 2 and 3). This condition ordinarily reaches its maximum in twenty-four to forty-eight hours, after which it gradually fades, its final complete disappearance bearing definite relationship to the severity of the reaction.

Following the application of the scarification test, in from five to twenty hours, there develops immediately adjacent to the scar, a pinkish areola, which rapidly extends in an outward direction until its maximum is reached (from twenty-four to seventy-two hours) at which time there usually exists a central deep pink zone of varying diameter surrounded by a pale pink, indefinitely marginated area, generally more or less circular in shape. The central zone is elevated and indurated and in the severer reactions may be covered with minute vesicles, which occasionally coalesce (Figs. 4 and 5). This cutaneous reaction persists for varying periods of time, from four or five days to two weeks, depending on its degree of severity.

The reaction to the ointment test manifests itself by the development in a time varying from ten hours to three days, of a papulovesicular eruption, at the site of application, and may vary in the number of papules from one to several hundred. The appearance of the eruption is characteristic, the most minute papules having a vesicular appearance, a pinkish color, and an erythematous areola. The papules vary in diameter from 0.5 to 3 or 4 mm., the erythematous areola sometimes measuring from 6 to 8 mm. In the more profuse eruptions these areolas may coalesce, giving a more or less pinkish hue to the entire area (Figs. 6, 7 and 8). In its severer types it usually persists for a week or ten days, after which the pigmented appearance may persist for several weeks, finally disappearing by a process of desquamation.

In describing the physical characteristics of these reactions, for the sake of clearness and uniformity, we have indicated three degrees for each, between which extremes we are enabled to classify all of our cases. In this classification we have followed closely the suggestion of Baldwin for the eye test and have used for the expression of these various degrees the single, double and triple plus marks which he has recommended.

In the interpretation of the eye reaction our single plus mark indicates all manifestations from a moderate redness of the inferior palpebral conjunctiva or of the semilunar fold or the caruncle up to a fairly marked injection of all of these tissues, with or without slight lachrymation or fibrinous exudation. The double plus mark covers the cases in which there occurs in addition to the above, mild capillary injection of the orbital conjunctiva, giving rise to a pinkish hue, some swelling of the caruncle, semilunar fold and palpebral conjunctiva, attended with lachry-

I. CASES IN WHICH THERE WERE NO CLINICAL EVIDENCES OF TUBERCULOSIS.

Case.	Name.	Age.	Clinically Non-tuberculous.	Test Applied.	Dose. Per cent.	Pos. + Neg. −	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction.	Remarks.
1	J. F.....	4	General nutrition poor; rachitis, adenoids, anemia.	Conj.....	0.5.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut.....	.....	−	....	−					
2	J. McG....	5	Good health.	Conj.....	0.5.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut.....	.....	−	....	−					
3	R. C.....	3	General nutrition poor.	Conj.....	0.5.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut.....	.....	−	....	−					
4	A. H.....	5	General nutrition good.	Conj.....	0.5.....	+	19	+.....	None.....	Neg.....	None.....	None.	The Scar. and Oint. tests were applied but the child was removed from the Home before reactions had time to appear.
				Scar.....	.....	..	..	.....	.....	.....	"	"	
				Oint.....	.....	..	..	.....	.....	.....	"	"	
				S. Cut.....	.....	+	..	+.....	.....	.....			
5	M. McG..	3	General nutrition fair.	Conj.....	0.5.....	−	..	−					
				Scar.....	.....	−	..	−					
				Oint.....	.....	−	..	−					
				S. Cut.....	.....	−	..	−					
6	G. B.....	3	General nutrition fair.	Conj.....	0.5.....	+	22	+.....	None.....	Neg.....	None.....	None.	
				Scar.....	.....	+	23	++(15x15)..	"	"	"	"	
				Oint.....	.....	+	51	+(28).....					
				S. Cut.....	.....	+	..	+.....					
7	T. S.....	3	General nutrition fair; slight adenitis.	Conj.....	0.5.....	+	32	++.....	None.....	Neg.....	None.....	+	
				Scar.....	.....	+	29	+ (10x10).	"	1 papule.....	"	+++	
				Oint.....	.....	+	29	+ (11).....			"		
				S. Cut.....	.....	+	..	+.....					
8	L. R.....	4	Rachitis; general nutrition fair.	Conj.....	0.5.....	+	21	++.....	Photophobia....	Neg.....	Unilateral conj. severe for 1 week after test.	++	
				Scar.....	.....	+	48	+ (12x12).	None.....	"	None.....	++	
				Oint.....	.....	+	112	+ (14).....	"	"	"	++	
				S. Cut.....	.....	+	....	+.....	.....	.....			

9	M. M.	5	General nutrition fair.	Conj.	1st dose 0.5 2nd " 0.75	+	48	++	None	Neg.	None	+	
				Scar		+	48	++ (20x20)	"	"	"	+	
				Oint		+	48	++ (25)	"	"	"	+	
				S. Cut		+	....	++			"		
10	W. C.	4	General nutrition fair.	Conj	0.5	+	23	+++	Photophobia	Neg.	None	+	
				Scar		+	24	++ (10x10)	None	"	"	+	
				Oint		+	24	+ (3)	"	"	"	+	
				S. Cut		+	....	++			"		
11	E. E.	6	General nutrition good.	Scar		—	....	—					
				Oint		—	....	—					
				S. Cut		—	....	—					
12	W. P.	3	General nutrition fair; adenitis.	Conj.	0.5	+	28	+	None	Neg.	None	+	
				Scar		+	24	+ (6x6)	"	"	"	+	
				Oint		+	48	++ (30)	Itching	"	"	+	
				S. Cut		+	....	++			"		
13	J. P.	3½	General nutrition fair; rachitis.	Conj.	0.5	+	50	+	None	Neg.	None	+	
				Scar		+	24	+ (3x4)	"	"	"	+	
				Oint		+	24	+ (4)	"	"	"	+	
				S. Cut		+	....	+	"		"		
14	D. M.	3	General nutrition fair.	Conj.	1st dose 0.5 2nd " 0.75	+	24	+	None	Neg.	None	+	
				Scar		+	28	+	"	"	"	+	
				Oint		+	48	++ (20)	"	"	"	+	
				S. Cut		+	....	+	"		"		
15	G. Y.	4	General nutrition fair.	Conj.	1st dose 0.5 2nd " 0.75	+	22	+	None	Neg.	None	+	
				Scar		+	24	+ (6x6)	"	"	"	+	
				Oint		+	22	+ (4)	"	"	"	+	
				S. Cut		+	....	++	"		"		
16	J. K.	3	General nutrition good; rachitis.	Conj	0.5	+	32	+	None	Neg.	None	+	
				Scar		+	40	+++ (25x20)	"	"	"	+	
				Oint		+	40	++ (30)	"	"	"	+	
				S. Cut		+	....	++	"		"		
17	W. C.	6	General condition fair.	Scar		+	28	+ (15x10)	None	Neg.	None	+	
				Oint		+	52	+ (10)	Itching	"	"	+	
				S. Cut		+	....	++			"		
18	J. G.	4	Rachitis; adenoids.	Conj		+	24	+	None	Neg.	None	+	
				Scar		+	24	+ (3x3)	"	"	"	+	
				Oint		+	41	+ (18)	"	8 Papules	"	+	
				S. Cut		+	....	+++	"		"		
19	A. K.	7	General nutrition fair.	Conj	1st dose 0.5 2nd " 0.75	+	23	+	None	Neg.	None	+	
				Scar		+	42	+ (10x10)	"	"	"	+	
				Oint		+	42	+	Itching	1 Papule.	"	+	
				S. Cut		+	....	++			"		
20	T. C.	5	General nutrition good.	Conj.	0.5	+	24	+	None	Neg.	None.		
				Scar { Human		+	48	+	"	"	"		
				Scar { Bovine		+	48	+	"				
				Oint		+	48	+ (13)	Itching	"	"		
				S. Cut		+	....	++	Inguinal glands enlarged l. side.	"	"		

I (Continued). CASES IN WHICH THERE WERE NO CLINICAL EVIDENCES OF TUBERCULOSIS.

Case.	Name.	Age.	Clinically Non-tuberculous.	Test Applied.	Dose. Per cent.	Pos. Neg.	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction.	Remarks.
21	R. F.	7	General nutrition fair.	Conj.	0.5	+	24	++	None	Neg.	None.	+	
				Scar { Human		+	48	++	"	"	"	+	
				Scar { Bovine		+	48	+		"	"		
				Oint.		+	48	++ (50)	Itching	"	"	+	
				S. Cut.		+		+	Inguinal glands enlarged l. side.	"	"		
22	J. K.	7	General nutrition fair.	Conj.	0.5	+	24	+	None	Neg.	None.		
				Scar { Human		+	48	++ (25x25)	"	"	"		
				Scar { Bovine		+	48	++ (20x20)	"	"	"		
				Oint.		+	....	+++ (100)					
				S. Cut.		+	....	+	Slight enlargement inguinal glands, left.				
23	A. P.	6	General nutrition good.	Conj.	0.5	+	25	++	None	48 hrs. O. S. same as O. D.	None.	—	
				Scar { Human			120	+ (8x13)	"	Neg.	"	—	
				Scar { Bovine		+	120		"	"	"	—	
				Oint.		+	73	+ (1x7)	"	"	"	—	
				S. Cut.		—	....	++ (30)				—	
24	J. S.	7	General nutrition fair.	Conj.	0.5	+	48	+	None	In 48 hrs. same as other eye.	None.	+	
				Scar { Human		+	24	+ (5x5)	"		"	—	
				Scar { Bovine		+	24	+ (3x3)				—	
				Oint.		+	48	+ (20)	"	Neg.	"	—	
				S. Cut.		+	....	+			"		
25	E.	3	Pertussis with broncho-pneumonia.	Conj.	1st dose 0.5 2nd " 0.75	+	24	+	None	Neg.	None		Both eyes instilled: both reacted.
				Scar.		+	24	++ (20x15)	"	"	"		
				Oint.		+	24	++	"	"	"		
26	M. M.	5	Bronchopneumonia.	Conj.	0.5	+	48	+					
				Scar. { Human		+	36	+ (5x15)					
				Scar. { Bovine		+	36	+ (5x5)					
27	J. S.	3	Pertussis.	Conj.	0.5	—	....	—					
				Scar.		—	....	—					
				Oint.		—	....	—					
28	L. M.	⅔	Bronchopneumonia.	Conj.	0.3	—	....	—					
				Scar.		—	....	—					
29	W.	2½	General nutrition fair.	Scar.		—	....	—					
				Oint.		—	....	—					
30	J. S.	1⅓	General nutrition poor.	Conj.	0.3	—	....	—					
				Scar.		—	....	—					
				Oint.		—	....	—					

31	R. C.....	1 1/6	General nutrition poor.	Conj.....	0.3.....	—	....	—.....	None	Neg.....	None.		
				Scar.....	.....	+	23	+ (10x10)....	"	"	"		
				Oint.....	.....	+	48	+ (15).....	"	"	"		
32	C.....	1½	General nutrition fair.	Conj.....	0.3.....	+	27	++.....	None	Neg.....	None.		
				Scar.....	.....	+	23	++ (20x10)..	"	"	"		
				Oint.....	.....	+	49	+ (8).....	"	"	"		
33	A. W....	2	General nutrition poor.	Conj.....	0.3.....	+	24	+.....	None	Neg.....	None.		
				Scar.....	.....	+	48	+ (10x18)....	"	"	"		
				Oint.....	.....	+	48	+++ (250+)	Itching.....	"	"		
34	T. R.....	1¼	General nutrition fair.	Conj.....	0.3.....	—	....	—					
				Scar.....	.....	—	....	—					
				Oint.....	.....	—	....	—					
35	A. C.....	2½	General nutrition good.	Conj.....	0.3.....	—	....	—					
				Scar.....	.....	—	..	—					
				Oint.....	.....	—	....	—					
36	J.....	3	General nutrition good; rachitis.	Conj.....	0.5.....	+	96	++.....	None	Neg.....	None.		
				Scar.....	.....	+	48	+ (10x10)....	"	"	"		
				Oint.....	.....	+	48	+ (8).....	"	"	"		
37	L.....	2	General nutrition fair.	Conj.....	0.3.....	—	....	—					
				Scar.....	.....	—	....	—					
				Oint.....	.....	—	....	—					
38	E. C.....	4	General nutrition good.	Conj.....	0.5.....	+	20	+.....	None	Neg.....	None.....	—	
				Scar. } Human	.....	+	48	++ (17x15)..	"	"	"	+	
				Scar. } Bovine	.....	+	48	++ (10x12)..	"	"	"	—	
				Oint.....	.....	+	48	+ (16).....	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	"	"	"	—	
39	T. G.....	6	Slight cervical adenitis; adenoids.	Conj.....	0.75.....	—	....	—.....	None	Neg.....	None.....	—	
				Scar.....	.....	+	26	+ (10x16)....	"	"	"	—	
				Oint.....	.....	+	....	+ (8).....	"	"	"	—	
				S. Cut.....	.....	+	....	+.....	"	"	"	—	
40	K. S.....	4	General nutrition poor.	Conj.....	0.75.....	+	25	+.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	30	+.....	"	"	"	+	
				Oint.....	.....	+	48	+ (15).....	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	"	"	"		
41	B. F.....	6	General nutrition good.	Conj.....	0.75.....	+	36	+.....	None	Neg.....	None.		
				Scar.....	.....	—	....	—.....	"	"	"	—	
				Oint.....	.....	+	....	+ (5).....	"	"	"	—	
				S. Cut.....	.....	+	....	+.....	"	"	Inguinal glands, both sides, enl'rged and tender.	—	
42	M. S.....	7½	General nutrition fair.	Conj.....	0.5.....	+	28	++.....	Pain in Eye.....	Neg.....	None.....	+	Bovine showed a few scattered papules.
				Scar. } Human	.....	+	48	+.....	None	"	"	+	
				Scar. } Bovine	.....	+	48	++ (15x15)..	"	"	"	+	
				Oint.....	.....	+	72	+++.....	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	"	"	"		
43	A. H.....	4	General nutrition fair.	Conj.....	0.75.....	+	31	+++.....	None	Neg.....	None.....	—	
				Scar.....	.....	+	24	++.....	"	"	"	+	
				Oint.....	.....	+	48	+.....	"	"	"	—	
				S. Cut.....	.....	+	....	+.....	"	"	Inguinal glands slightly enlarged.	—	

I (CONTINUED). CASES IN WHICH THERE WERE NO CLINICAL EVIDENCES OF TUBERCULOSIS.

Case.	Name.	Age.	Clinically Non-tuberculou .	Test Applied.	Dose. Per cent.	+ Pos. − Neg.	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction.	Remarks.
44	F. C.....	2	General nutrition good.	Conj.....	0.3.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
45	A. G.....	2	General nutrition poor; rachitis.	Conj.....	0.3.....	+	28	+ (15x15)..	None.....	Congested....	None.		
				Scar.....	.....	+	24	+ (15x15)..	"	Neg.....	"		
				Oint.....	.....	+	24	+ (11).....	"	"	"		
46	A. C :...	3	General nutrition poor; rachitis.	Conj.....	0.3.....	+	28	+ (20x20)	None.....	Neg.....	None.		
				Scar.....	.....	+	23	+ (20x20)	"	"	"		
				Oint.....	.....	+	48	+ (50)..	"	"	"		
47	W.	2	General nutrition poor	Conj.....	0.3.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
48	T. K.....	2	General nutrition fair.	Conj.....	0.3.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
49	A. W	5	General nutrition fair.	Conj.....	0.75.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut.....	.....	−	....	−					
50	K. S.....	6	General nutrition poor.	Conj.....	1st dose 0.5	+	20	+	None	Neg.....	None.....	+	
					2nd " 0.75								
				Scar.....	.....	+	....	+ (6x6).....	"	"	"	−	
				Oint.....	.....	+	....	+ (6).....	"	"	"	+	
				S. Cut.....	.....	+	....	+	"	"			
51	E. K.....	6	General nutrition poor.	Conj.....	0.5.....	−	....	−					
				Scar.....	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut.....	.....	−	....	−					
52	J. L.	5	General nutrition good.	Conj.....	0.75.....	+	20	+	None	Neg.....	None.....	−	
				Scar.....	.....	+	49	+ (6x4).....	"	"	"	−	
				Oint.....	.....	+	48	+ (17).....	"	"	"	−	
				S. Cut.....	.....	+	....	+	"	"			
53	D.A. (Col)	6	General nutrition poor.	Conj.....	0.5.....	−	....	−					
				Scar. { Human / Bovine	.....	−	....	−					
				Oint.....	.....	−	....	−					
				S. Cut..	.....	−	....	−					

54	S. M.....	7	General nutrition fair; adenitis.	Conj.....	0.5.....	+	27	+.....	None	Neg.....	None.....	+
				Scar. { Human / Bovine	.....	+	23	++ (30x20)	"	"	"	+
						+	48	+ (7x5).....	"	"	"	
				Oint.....	.....	+	48	+++ (50)...	"	"	"	
				S. Cut.....	.....	+	....	+.....				
55	M. C.....	6	General nutrition fair; adenitis	Conj.....	0.5.....	+	24	++.....	None	Neg.....	None.....	
				Scar.....	.....	+	25	+ (10x10).....	"	"	"	
				Oint.....	.....	+	29	+ (7).....	"	"	"	
				S. Cut.....	.....	+	....	+.....	"	"	"	
56	M. D.....	7	General nutrition poor.	Conj.....	0.5.....	+	26	+.....	None	Neg.....	None.....	
				Scar. { Human / Bovine	.....	+	53	++ (10x15)...	"	"	"	+
							....	.....	"	"	"	
				Oint.....	.....	+	120	++ (60)...	"	"	"	
				S. Cut.....	.....	+	....	+.....				
57	C. J.....	5	General nutrition good.	Conj.....	0.5.....	—	....	.....	None			
				Scar. { Human / Bovine	.....	—	....	—				
						—	....	—				
				Oint.....	.....	—	....	—				
				S. Cut.....	.....	—	....	—				
58	A. C.....	5	General nutrition poor; adenitis.	Conj.....	0.75.....	+	25	++.....	Photophobia....	Neg.....	None.....	+
				Scar.....	.....	+	25	++ (15x17)...	None	"	"	+
				Oint.....	.....	+	46	+ (5).....	"	"	"	
				S. Cut.....	.....	+	....	+.....	"	"	"	
59	M. C.....	3	General nutrition poor; rachitis.	Conj.....	0.5.....	+	32	+++.....	Photophobia....	Neg.....	{ Phlyct keratitis, central corneal ulcer 8 days after 5 phlyctenulæ about 8 days aft. test. Recovery and relapse.	
				Scar.....	.....	+	28	+++ (25x22)	None	"		
				Oint.....	.....	+	52	+++ (250+)	Itching.....	"		
60	M. F.....	4	General nutrition fair.	Conj.....	0.75.....	+	25	+++.....	Photophobia & pain in eye.....	Neg.....		
				Scar.....	.....	+	20	++ (20x15)...	None	"		
				Oint.....	.....	+	24	+++ (250+)	"	"	None.	
61	G. B.....	7	General nutrition poor.	Conj.....	0.5.....	+	23	+.....	None	Neg.....	None.	
				Scar. { Human / Bovine	.....	+	48	++ (18x17)...	"	"	"	
						+	48	+ (10x10).....	"			
				Oint.....	.....	+	96	++ (100)...	"	"	"	
62	A. P.....	6	General nutrition fair.	Conj.....	0.5.....	+	28	++.....	Photophobia....	Neg.....		
				Scar. { Human / Bovine	.....	+	28	+++ (25x25)	None	"	Phlyctenulæ 9 days after test; recovery and recurrence.	
						+	28	+ (15x15).....	.....	"		
				Oint.....	.....	+	28	++ (100)...	"	2 papules.		
63	E. McF..	5	General nutrition fair.	Scar. { Human / Bovine	.....	—	....	—				
						—	....	—				
				Oint.....	.....	—	....	—				
64	V. C.....	4	General nutrition fair.	Conj.....	0.75.....	+	30	+++.....	Pain in Eye.....	Neg.....	None.	
				Scar.....	.....	+	21	+++ (28x28)	None	"	"	
				Oint.....	.....	+	48	++ (20).....	"	"	"	
65	M. K.....	7	General nutrition fair.	Conj.....	0.5.....	+	26	++.....	None	Neg.....	None.....	+
				car. { Human / Bovine	.....	+	50	+++ (30x30)	"	"	"	+
						+	50	++ (10x15)...	"	"		
				Oint.....	.....	+	26	+ (8).....	"	"	"	+
				S. Cut.....	.....	+	....	+.....	"	"	"	+

I (Continued). CASES IN WHICH THERE WERE NO CLINICAL EVIDENCES OF TUBERCULOSIS.

Case.	Name.	Age.	Clinically Non-tuberculous.	Test Applied.	Dose. Per cent.	Pos. + Neg. −	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction.	Remarks.
66	M. Y.	6	General nutrition fair.	Conj.	0.5	−	....	−					
				Scar.		−	....	−					
				Oint.		−	....	−					
				S. Cut.		−	....	−					
67	H. G.	4	General nutrition fair.	Conj.	0.75	−	....	−					
				Scar.		−	....	−					
				Oint.		−	....	−					
				S. Cut.		−	....	−					
68	L. F.	7	General nutrition good.	Conj.	0.5	+	29	++	None	Neg.	None.	+	Mother dead of tuberculosis.
				Scar. Human		+	48	+++ (30x20)				+	
				Scar. Bovine		+	48	++ (10x12)				+	
				Oint.		+	96	+++ (100)				+	
				S. Cut.		+	....	++				+	
69	J. de H.	5	General nutrition fair; rachitis.	Conj.	1st dose 0.5 2nd " 0.75	+	23	++	None	Neg	None.	+	
				Scar		+	28	++ (20x17)	"	"	"	+	
				Oint.		+	52	+ (7)	"	"	"		
				S. Cut.		+	..	+++	"	"	"		
70	A. D.	6	General nutrition fair; (enlarged tonsils).	Conj.	0.5	+	24	+	None	Neg.	None.		
				Scar.		+	20	+	"	"	"	+	
				Oint.		+	28	+ (14)	"	"	"	+	
				S. Cut.		+	....	+	"	"	"		
71	M. H.	4	Bronchitis; general adenitis.	Conj.	1st dose 0.5 2nd " 0.75	+	24	+	None	Neg.	None.	+	
				Scar.		+	....	+	"	"	"	+	
				Oint.		+	24	+ (4)	"	"	"	++	
				S. Cut.		+	....	++	"		"		
72	J. K.	5	Rachitis.	Conj.	1st dose 0.5 2nd " 0.75	−	....	−					
				Scar.		−	....	−					
				Oint.		−	....	−					
				S. Cut.		−	....	−					
73	M. W.	3	General nutrition poor; rachitis.	Conj.	0.5	−	....	−					
				Scar.		−	....	−					
				Oint.		−	....	−					
				S. Cut.		−	....	−					
74	S. M.	5	General nutrition fair.	Conj.		+	28	++	Photophobia	Neg.	Phlyct. conjunc.		
				Scar.		+	73	++ (14x14)	None	"	corneal ulcers 10		
				Oint.		+	24	+ (3)	"	"	days after test.		

75	M. D....	3	General nutrition fair.	Conj.....	....	+	23	+.....	None	Neg.....	None.	.....	Unilateral simple conjunc. 6 days after, lasting 1 week. Eye had practically returned to normal.
				Scar.....	.....	+	43	+.....	"	"	"		
				Oint.....	.....	+	22	+ (12).....	Itching.....	"	"		
76	F. M.....	4	General nutrition fair; rachitis.	Conj.....	0.5	+	24	+..:	None	Neg	None.		
				Scar.....	.....	—	....	—.....	"	"	"		
				Oint.....	.....	+	28	++ (30).....	Itching.....	"	"		
77	C. C.....	5	General nutrition fair.	Conj.....	0.5	—	....	—					
				Scar.....	.....	—	....						
				Oint.....	.....	—	....	—					
78	D. W....	2½	Athrepsia	Conj.....	0.5	—	....	—.....	.....	.....	.....	.....	Mother had tuberculosis when infant was born.
				Scar.....	.....	—	....						
				Oint.....	.....	—	....						
				S. Cut.....	.....	—	....	—					
79	R. S.....	5 6	General nutrition poor; adenitis.	Conj.....	0.5	—	....	—					
				Scar.....	.....	—	....						
				Oint.....	.....	—	....						
				S. Cut.....	.....	—	....	—					
80	J. D....	2	Acute bronchopneumonia.	Conj.....	0.5	—	....	—					
				Scar.....	.....	—	.. ..						
				Oint.....	.....	—	....						
81	W. F....	3½	Acute cervical adenitis.	Conj.....	0.5	—	....	—					
				Scar.....	....	—	....						
				Oint.....	.....	—	....	—					
82	J. L.....	1½	General nutrition poor.	Conj.....	0.5	—	....	—					
				Scar.....	.....	—	....						
				Oint.....	.....	—	....						
				S. Cut.....	.....	—	....	—					
83	E.D.(Col)	1½	General nutrition poor.	Conj.....	0.5	—	....	—					
				Scar.....	.....	—	....						
				Oint.....	.....	—	....						
				S. Cut.....	.....	—	....	—					
84	M. B.....	1¼	Enterocolitis ...	Conj.....	0.3	—	....	—.....					
85	G. C.....	5	Fair health	Conj.....	0.5	+	24	++.....	None	Neg.....	Sev. conjunctivitis appearing 96 hrs.; continuing 2 weeks.		
86	S. W.....	1½	Mild rachitis ...	Conj.....	0.3	—	....	—.....	.....	.....	.....		
87	E. I.....	3	Fair health	Conj.....	0.5	+	21	+.....	None	Neg.....	None.		
88	A. K.....	6	Good health	Conj.....	0.5	+	36	+.....	None	Neg.....	None.		
89	W. G.....	10	Acute articular rheumatism.	Conj.....	1	+	18	+.....	Recurrence of joint pain	Slight inflammation.	None.		
90	K. O'D .	8	Bronchopneumonia	Conj.....	1	+	29	+.....	None	Slight inflammation.	None.		
91	H. T....	8	Chorea & acute rheum. and endocarditis.	Conj.....	1	+	24	+.....	None.....	Neg.....	None.		
92	J. McK ..	10	Typhoid fever ..	Conj.....	1	—	....	—.....	.....	.....	.....	.....	Conj. test applied at height of fever. Other tests in afebrile stage.
				Scar.....	.....	—	....						
				Oint.....	.....	—	....	—					
93	A. H.....	9	Lobar pneumonia	Scar.....	.....	—	....	—					
				Oint.....	.....	—	....						

I (Concluded). CASES IN WHICH THERE WERE NO CLINICAL EVIDENCES OF TUBERCULOSIS.

Case.	Name.	Age.	Clinically Non-tuberculous.	Test Applied.	Dose. Per cent.	Pos. + Neg.	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction.	Remarks.
94	H. S.	21 m.	Bronchopneumonia.	Conj.	1st dose 0.5 2nd " 0.75	—	..	—		Neg.			2 conj. tests made during febrile period. The others in afebrile period.
				Scar.		+	23	++ (12x12)	None	"	None.		
				Oint.		+	23	++ (20)	"	"	"		
95	K. McD.	2½	Bronchopneumonia.	Conj.	0.5	—	..	—					Eye test applied during febrile period; others during afebrile period.
				Scar.		—	....	—					
				Oint.		—	....	—					
96	P. W.	2	Pertussis complicated by bronchopneumonia; tetany.	Conj.	0.5	—	....	—					
				Scar.		—	....	—					
				Oint.		—	....	—					
97	E. W.	1⅔	Pertussis with extreme secondary anemia.	Conj.	0.5	+	24	++	None	Neg.	None.		This child reacted in the presence of extremely marked anemia.
				Scar.		+	24	++ (10x15)	"	"	"		
				Oint.		+	24	+++ (100)	"	"	"		
98	M. H.	1½	Cervical lymphadenitis (acute).	Conj.	0.3	+	....	++	None	Neg.	None.		
				Scar.		+	24	++ (20x15)	"	"	"		
				Oint.		+	48	++	"	"	"		
99	W. M.	7 12	Bronchopneumonia.	Conj.	0.3	—	....	—					
100	J. B. H.	⅓	Acute otitis media; marasmus.	Conj.	0.3	+	....	+	None	Neg	None.		
101	S. C.	4	Broncho, neumonia.	Conj.	0.75	—	....	—					Tests were applied within 8 days of death.
				Scar.		—	....	—					
				Oint.		—	....	—					
102	F. W.	2	Bronchopneumonia with pertussis.	Conj.	1st dose 0.5 2nd " 0.75	—	....	—					
				Scar.		—	....	—					
				Oint.		—	....	—					
103	J. C.	1½	Bronchopneumonia.	Conj.	1st dose 0.5 2nd " 0.75	—	....	—					Child anemic and emaciated. Test applied 3 days before death.
104	M. N.	2½	Follicular enteritis.	Conj.	1st dose 0.5 2nd " 0.75	—	....	—					Post mortem showed no evidence of tuberculosis.
105	J. M.	1½	Pertussis.	Conj.	0.5	—	....	—					Post mortem showed no evidence of tuberculosis.
106	K. B.	1½	Marasmus.	Conj.	0.5	—	....	—					Post mortem showed no evidence of tuberculosis.
107	W. H.	7	Typhoid Fever.	Conj.	1	+	24	++	None	Neg.	None.		Eye test during height of fever; scar. and oint. during convalescence.
				Scar.		+	....	+	"	"	"		
				Oint.		+	....	++	"	"	"		
108	L. S.	6	Acute articular rheumat. with acute endocarditis.	Scar.		—	....	—					
				Oint.		—	....	—					
109	T. F.	2	Typhoid fever, otitis media, multiple neuritis.	Conj.	0.5	—	....	—					
				Scar.		—	....	—					
				Oint.		—	....	—					
110	M. K.	4	General nutrition fair.	Conj.	0.75	+	24	++	None	Neg.	None.	+	
				Scar.		+	48	++ (15x15)	"	"	"	—	
				Oint.		+	43	+	"	"	"		
				S. Cut.		+	....	++	"	"			

mation and fibrinous or fibropurulent discharge. The triple plus mark indicates all grades of reaction from the foregoing up to the most severe, as described in the above general description of the eye reaction.

In the description of the cutaneous reaction, the single plus mark indicates any degree of hyperemia up to a diameter of 10 mm. The double plus mark indicates all degrees of hyperemia having diameters of from 10 to 20 mm. and the triple plus mark, all reactions having diameters of more than 20 mm.

In the case of the ointment reaction the single plus mark indicates an eruption of from one to twenty papules; the double plus mark, from twenty to sixty papules, and the triple plus mark, fifty or more papules.

MATERIAL USED.

Practically all our patients were under 8 years of age and all but twenty-six of them were inmates of St. Vincent's Home, an institution with a population of about 400, composed of foundlings, orphans and destitute children. The cases in the home were tested in routine by wards, irrespective of the conditions from which they were suffering, and in the great majority of instances, without any knowledge of their physical condition prior to or at the time the tests were applied. We purposely deferred the physical examination of these children until after the tests had been applied, for two reasons, first, in order to be unbiased in our interpretation of the results, and second, in order to make ourselves especially vigilant in searching for tuberculous lesions in those who reacted. We had the children under absolute control throughout the entire period that the tests were being made, a special nurse having been employed for their exclusive care.

The accompanying tables, which record our results, are self-explanatory.

SUMMARY OF TABLES.

In addition to the cases designated in the tables, we have applied the test to seventeen infants ranging in age from four weeks to five months. All three tests were applied to six of them, the scarification test to all, and the ointment to but fourteen. Inflammatory conditions of the abdomen interfered with the application of the eye and ointment tests to the entire group. The results were entirely negative. Tuberculosis was not suspected in any of the cases and in about half of them the condition of nutrition was fair; in the remainder poor.

Of the 134 patients resident in St. Vincent's Home, 95 were clinically non-tuberculous, 27 had suspicious signs of either pulmonary or glandular tuberculosis, and 12 were definitely tuberculous. Of the 95

clinically non-tuberculous patients, 59, or 62.1 per cent., reacted; of the 27 suspicious patients, 23, or 85.1 per cent.; and of the 12 tuberculous, all, or 100 per cent.

Of the 26 patients outside of St. Vincent's Home, 15 were clinically non-tuberculous, 1 suspicious, and 10 tuberculous. Of the clinically non-tuberculous patients 5, or 33⅓ per cent., reacted. The 1 suspicious subject failed to react and, of the 10 tuberculous patients, 9, or 90 per cent. reacted. The one suspicious case in this latter group was probably one of tuberculous meningitis; the patient was tested within the last twenty-four hours of life. The one tuberculous patient who failed to react had advanced pulmonary tuberculosis and was anemic and emaciated.

Taking the two groups together, there were 110 clinically non-tuberculous, 28 suspicious and 22 tuberculous. Of the clinically non-tuberculous, 64, or 58.2 per cent. reacted positively; of the suspicious patients 23, or 82.1 per cent. reacted positively, and of the tuberculous 21, or 95.4 per cent. reacted positively.

If to these groups are added the 17 infants who were non-tuberculous clinically, and all of whom failed to react, the only change that occurs is in the non-tuberculous column in which the percentage of positive reactions is reduced from 58.2 to 51.2 per cent.

One thing that is especially noticeable in these results is the high percentage of positive reactions among the inmates of St. Vincent's Home. This result is in no sense surprising, since the institution is enormously overcrowded, and, until very recently, from the early winter until the late spring, its inmates have been housed with the windows closed and the wards sometimes overheated and sometimes underheated, depending largely on the external temperature. Scattered throughout the various wards there are a number of definitely tuberculous children and a fairly large number that might be suspected of tuberculosis, who would act as especially effective foci in a community of individuals with as marked lowering of the general nutrition as these children show.

OBSERVATIONS OF REACTIONS.

Following in the footsteps of others, we studied our earlier cases from hour to hour, to determine the time of beginning, the maximum point of and the length of duration of the reactions, but, finding that there was nothing to be gained from these frequent observations, we later abandoned them. We are satisfied if observations are made at the end of twelve hours, twenty-four hours, and forty-eight hours, and after this time, the cases are kept under general supervision, that no reactions will be overlooked and all essential information will be obtained. The mildest

cutaneous and ointment reactions will never be missed and we have never observed an eye reaction which did not persist long enough to be discovered during such observation periods.

Nevertheless, even in our later cases, we had observations made at fairly frequent intervals, in order to get a general idea of the course of the various reactions. The earliest onset of the conjunctival reaction occurred two and one-half hours after instillation and the latest forty-eight hours after instillation. In two cases the onset of the cutaneous reaction occurred five hours after its application, and in two cases it did not appear until the forty-eighth hour. The earliest onset of the ointment reaction was ten hours after it was applied and the latest seventy-two hours.

The earliest maximum conjunctival reaction was eleven and one-half hours after instillation and the latest ninety-six hours. The average was twenty-eight hours. For the cutaneous reaction, the earliest was twenty hours and the latest one hundred and twenty hours, the average being thirty-six hours. For the ointment test, the earliest was twenty-two hours, the longest one hundred and twenty hours, and the average forty hours.

As to the length of duration of the various reactions, our observations are accurate only insofar as they show that in one case the conjunctival reaction ceased in nineteen and one-half hours and that in several instances it did not entirely disappear for a period varying from seven to nine days; that the shortest duration of the cutaneous reaction was forty-eight hours, and that it sometimes persisted for more than ten days; and that the shortest duration of the ointment reaction was forty-eight hours and the longest more than ten days, it always having faded in color and most of the papules having disappeared at this time.

CONTROL TESTS.

The controls were practically negative in all cases, except in a few eye cases, to be referred to, in one scarification case, and in eleven of the ointment cases. In each of the latter two this was due to contamination from the inoculated areas. The control in the scarification cases was the middle scar, about 5 cm. from each of the others. Whilst the solution was drying, the child evidently transferred some of it to the control with its fingers. In the case of the ointment it was not removed from the abdomen and consequently when the undershirt was replaced it spread the ointment beyond the limits to which it had been applied, in some cases extending to the control areas.

SUBJECTIVE SYMPTOMS.

Very few of the children complained of discomfort from the reactions, none from the cutaneous. In fourteen of the ointment cases there was evidence of itching. In the conjunctival cases complaint of pain in the eyes was made in six cases; photophobia and recurrence of joint pains occurred in one case of rheumatism and photophobia was noted in thirteen other cases. One of the patients who reacted positively to the subcutaneous test complained of pain at the site of injection; another with chronic tubercular arthritis of the knee had an access of pain in this joint and severe abdominal pain (possibly due to a stirring up of tuberculous mesenteric glands) and a third patient had enlarged painful and tender inguinal glands with pain at the point of injection.

DILATATION OF THE PUPILS.

Apropos of the observation of Blum that dilatation of the pupils followed from one and one-fourth to one and one-half hours after the instillation of the eye, we made observations in the last twenty cases tested and found the pupil of the instilled eye dilated in five cases, contracted in four, and without change in eleven. At various times, in our routine examinations, we had noted dilatation or contraction of the instilled pupils twelve hours or more after instillation. This phenomenon is interesting; especially our observation that sometimes the instillation is followed by contraction instead of dilatation.

We have no satisfactory explanation to offer, although it is possible that the inconstant pupil effects of the instillation of tuberculin depend not alone on any inconstant strength or concentration of the solution used, but on individual peculiarities of the eyes. Whether local irritation produced by the drug, greater in one instance and less in another, may be accountable for these pupil phenomena, is a subject for further investigation.

UNIFORMITY OF REACTION.

In about sixty of our cases the conjunctival test was applied from one to three weeks before the scarification and ointment tests. In the remainder of the cases the three tests were applied at the same time.

The conjunctival, scarification and ointment tests were all applied in 132 cases. In 122 of these all of the tests reacted positively. In the ten remaining, the conjunctival test was negative four times when both of the others were positive and positive once when both of the others were negative. The scarification test was negative four times when one or both of the others were positive, and the ointment three times. It will

be seen from these figures that there was almost absolute uniformity as to reaction with these three tests.

As to the relative degrees of reaction in the individual cases, the ointment test gave the most marked reaction in 35 cases, the conjunctival in 32 cases, and the scarification test in 24 cases. This result is very interesting in connection with the statements in the literature regarding the comparative sensitiveness of the conjunctival, scarification and ointment tests.

Wolff-Eisner, for instance, apparently working with weaker solutions, expresses the opinion that the scarification test is more sensitive than the conjunctival, and that it shows latent foci which are not revealed by the conjunctival unless repeated and that the cutaneous reaction is positive in one-half of all cases, while the conjunctival is positive in but one-sixth.

Feer found the conjunctival test very uncertain with a 0.5 per cent. solution, and frequently negative in cases which were positive to a 25 per cent. solution applied cutaneously.

Morelli, in 100 cases of pulmonary tuberculosis, obtained 98 positive reactions to the scarification and but 86 to the conjunctival test. In 22 cases of tuberculosis other than pulmonary, he obtained 72 per cent. of positive reactions to the scarification and 63 per cent. to the conjunctival. In 96 cases of non-suspected tuberculosis, he obtained 21 per cent. of positive reactions to the scarification, and 11 per cent. to the conjunctival test.

Stadelmann's figures correspond with Wolff-Eisner's, and they share the belief that the conjunctival reaction indicates an active tuberculous process, while the cutaneous suggests inactive or latent foci. A few investigators have found the reactions more uniform and Calmette inclines to the belief that tuberculous lesions are more frequently found by the conjunctival than by the scarification test.

Wolff-Eisner attempts to explain the greater sensitiveness of the scarification test by a difference between the abortive power of the skin and conjunctiva; the absorption in the skin being less, the concentrated tuberculin remains where it is applied until the cells, which, owing to the latent nature of the foci, have not reacted to tuberculin for a long time, regain their power to react under the influence of the prolonged stimulation, whereas in the conjunctiva, where absorption is rapid, the contact is not long enough to stimulate the formation of antibodies.

On the basis of our results, we can not share in this opinion, and, because of the almost absolute uniformity of reaction with the three tests, we believe that the apparent lessened sensititiveness of the conjunctiva is to be accounted for on some other basis. There must be some

satisfactory way to account for the differences which have been obtained by different investigators, and we suggest that it probably depends on the use of solutions of varying strengths which, in the case of the tuberculin precipitate, is due to defective technic in its preparation. In the description which we have given of this procedure, we have pointed out that the precipitate which forms after the concentrated tuberculin original has been added to the alcohol, should be separated from its supernatant liquid as soon as possible. If this is not done, the proteids of the peptones and beef extract contained in the media will be precipitated out and collected with the tuberculin. It is very evident that percentage solutions made from such a precipitate would be much weaker than corresponding percentage solutions prepared from a pure tuberculin precipitate. It is not unlikely also that the effect of too prolonged contact of the alcohol with the precipitated tuberculin may have the effect of denaturizing, and thus in part destroying the activity of the tuberculin, which is a proteid body.

We believe, therefore, that the differences in results which have been obtained can be obviated if proper care is practiced in the preparation of the solutions which are used, and that, as far as children are concerned, as has been shown by our results, there will be practically absolute uniformity of reaction to the various tests. The demonstration of this uniformity of reaction we consider one of the most important results of our investigation, since it shows that none of the three tests has any advantage, insofar as the sensitiveness to reaction is concerned. It then becomes a question as to which of the three is most desirable from other standpoints.

Before beginning the application of the conjunctival test, we had no knowledge of any serious results from its use. It is unquestionably much easier of application than the other tests, and it probably yields results a little more quickly, but it has the great disadvantage of producing a decidedly uncomfortable lesion, and it is not infrequently followed by serious inflammations of the eye, which not only produce great physical discomfort and require weeks of active treatment, but which may permanently affect the vision and even lead to its complete destruction. In our series we have had two cases of severe purulent unilateral conjunctivitis, six of severe recurring phlyctenular conjunctivitis, one of which developed corneal ulcers, and one case of keratocyclitis with a large central corneal ulcer. Permanent disturbance of vision is sure to follow in this last case from the central scar, even should the associated lesion, which at present is in a very unpromising condition, clear up eventually.

These results are by no means unique, many similar observations having been made. Thus Webster and Kilpatrick, Moro, Feer, Schenck, Eppenstein and Gaupp, in their reports, refer to ten cases of phlyctenules; Van Durme and Stocke report five and Schenck and Seifert and Krause and Hertel many of the same condition. Ebstein, de Lapersonne and Eppenstein report eight cases of keratitis; Heymann one case of iritis; Renon one case of kerato-iritis; Simonin one case of corneal ulcer; Buch one case of conjunctival hemorrhage; de Lapersonne two cases of iridocyclitis; Cassoute one case of serious eye trouble, causing loss of vision, and Barbier the case of a child in which an old bilateral keratitis, healed for one year, was stirred up by the instillation of tuberculin, continued for two months, and caused almost complete destruction of the sight of one eye. We have had a number of verbal reports of eye complications, some relating to very serious conditions, and we are sure they are much commoner than the references we have communicated would indicate.

While we are willing to admit the assertion of Calmette that many of the complications may be due to the reaction-inflammation paving the way for the development of preexisting or superadded infectious organisms, we do not feel that this in any sense justifies the test. In fact, we are strongly of the opinion that any diagnostic procedure which will so frequently result in serious lesions of the eye, irrespective of the way in which it produces them, has no justification in medicine, especially since there are other diagnostic tests of equal if not superior value, which are applicable to the same class of cases and not attended with the same disturbing results. We refer to the scarification and ointment tests. As to the relative merits of these two tests, we feel that the ointment offers the advantage of eliminating any denudation of the surface of the skin, thus lessening the danger of infection.

We have had no complaint and have noted no evidence of discomfort during the reaction to the scarification test and nothing other than itching during that to the ointment test. We have seen no complications from either, although we note in the literature that tuberculide (v. Pirquet); lichen scrofulosorum (Ferrand and Lemaire, von Pirquet, Baginsky and Siccard, Oppenheim); scrofuloderm (Moro and Doganoff); and lymphangitis with swelling of the epitrochlear glands (Wolff-Eisner, Kronig) have followed the scarification reaction, and lichen scrofulosorum (Moro) the ointment reaction.

In addition to this, Feer quotes Pfaundler, Moro and Doganoff as having "frequently observed phlyctenules" appear on the cornea ten or fifteen days after the application of the scarification test, which they attributed

to a special hypersensitiveness of the entire organism. Feer communicates two instances of his own, occurring in 344 applications of the cutaneous test, in one of which the conjunctival test had been applied ten days previously. It is not stated in his quotation whether the conjunctival test had been previously applied to the cases of the authors above mentioned. It would seem likely, from the period elapsing between the application of the conjunctival test and the occurrence of the phlyctenules in Feer's second case that the phlyctenules were attributable to the conjunctival rather than to the cutaneous test.

Wolff-Eisner refers to the occurrence of phlyctenules after the application of the scarification test, but, in making the statement he is evidently quoting from the observations of others. In any event, it is manifest from the reports in the literature that complications of this nature occur much more frequently after the eye test than after the scarification test. It is entirely reasonable that it should be so, since the direct application of the solution to the eye not only brings the conjunctival tissue in contact with a larger dose of the tuberculin, but produces an inflammatory lesion which renders the tissues of the eye more vulnerable to infectious organisms, which may be in the eye and which are undoubtedly responsible for many of the severe concomitant symptoms in these cases.

In our own cases the eye complications occurred in all but two before either the scarification or ointment tests had been applied. In these two the three tests were applied at the same time, and in them we have credited the results to the eye test.

If sensitization of the entire organism follows the application of the scarification test, as the authors quoted suggest, it is not surprising that phlyctenules should follow, since their occurrence has been noted after the subcutaneous test. In one of our own cases (Case 62), phlyctenules developed nine days after the subcutaneous injection, the conjunctival scarification and ointment tests having preceded the subcutaneous by more than one month.

It is very probable that the dosage used in the scarification test, the absorptive power of the skin in different individuals, as well as the manner of applying the test, especially the nature of the scarification, may have some bearing on this question. Generally speaking, we do not believe it probable that a systemic reaction is likely to follow the application of either the scarification or ointment tests. Thus the drop of 10 per cent. tuberculin which we applied to the skin in carrying out the scarification test was equal to 0.01 c.c., which contained exactly 0.001 gm. of tuberculin. The drop containing this 0.001 gm. was only in small part in contact with the point of scarification, the greater bulk of it being scat-

tered around its borders. Unless, therefore, it was absorbed by the unbroken skin, the absorptive properties of which we know to be but slight, the amount of actual tuberculin taken up by the tissues generally must have been exceedingly small; and when we realize that one-half of the total quantity of tuberculin contained in this drop was injected subcutaneously in several children who had reacted cutaneously without producing symptoms of systemic reaction, we feel that the chance of its occurrence after the cutaneous test must be extremely slight, or that if it does occur it represents an extraordinarily high degree of sensitiveness.

Furthermore, we believe that in the uninjured skin to which the ointment in the amount used, 0.15 gm. equivalent to 0.075 gm. of tuberculin, is applied, absorption of tuberculin sufficient to produce anything beyond a local reaction can not possibly occur.

LATE REACTIONS.

There is a certain peculiarity of the reaction, pointed out by Stadelmann, which is worthy of consideration and which seems to be common to all, namely, a tendency to be delayed in its development and persistent in its duration. This delayed reaction may follow in cases in which the primary reaction was early. In the case of the cutaneous reaction it may persist at its maximum for as long as three or four weeks. We have not noted what we felt might be termed a delayed reaction after any of our eye or scarification tests; but in one instance we had a persistence of the ointment reaction at its maximum for about three weeks. An effort has been made to explain this type of reaction on the basis of the histologic study of the papule. Daels examined four such papules from cadavers and one from a living subject. Some of these showed nothing specific, but in two cases the papule accurately reproduced the structure of the tubercle.

This histologic picture, which was discovered in very circumscribed areas by the examination of serial sections, made him suspect the presence of dead bacteria in the tuberculin, which suspicion he confirmed by studying the centrifugated sediment of the same tuberculin that had produced the lesions.

He does not suggest the presence of dead bacilli in the tuberculin as an explanation of the occurrence and genesis of the von Pirquet reaction, but makes the rather interesting observation that the presence of the bodies or fragments of the bodies of dead bacilli might throw some light on the return reactions which follow the subcutaneous test, as well as account for the eye reactions which sometimes occur in apparently healthy individuals when the test is repeated with a sufficiently large dose.

II. CASES IN WHICH THERE WERE PHYSICAL SIGNS SUGGESTING TUBERCULOSIS.

Case.	Name.	Age.	Suspected Tuberculosis	Test Applied.	Dose. Per cent.	Pos. Neg.	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reactions.	Remarks.
1	W. S....	4	Suspicious pulmonary tuberculosis (right apex).	Conj..... ...	0.5.....	+	75	++.....	None	Neg.....	Phlyct. keratitis 10 days after test; inflammation continued from beginning of reaction.	.....	After complication set in it was discovered he had had a previous attack.
				Scar.	.....	+	48	+ (9x8).....	"	"			
				Oint	.. ..	+	32	+++ (100)..	Itching.....	"			
2	A. F.....	6	Palpable mesenteric glands.	Scar. { Human	.....	+	50	+++ (25x25)	None	Neg.....	None.		
				Scar. { Bovine	.....	+	50	++ (15x10)..	"	"	"		
				Oint.....	.....	+	48	+++ (250+)	Itching.....	A few papules.			
3	H. C.....	6	Palpable mesenteric glands.	Conj.....	0.5.....	+	24	+.....	None	Neg.....	None.....	+	
				Scar.	.....	+	21	++ (15x10)..	"	"	"	+	
				Oint.	.....	+	44	++ (22).....	"	"	"	++	
				S. Cut.....	.....	+	....	+.....	"	"	"		
4	N. McC..	4	Palpable mesenteric glands.	Conj	0.5.....	+	28	+++.....	Pain in eye	Neg.....	None.....	+	
				Scar. { Human	.....	+	49	++ (25x20)..					
				Scar. { Bovine	.....	+	49	+ (7x9).....	None		"	+	
				Oint.	.....	+	41	+ (9).....	"	Neg.....	"	+	
				S. Cut.....	.....	+	....	++.....	"	"	"		
5	J. B.....	4	Suspicious pulmonary tuberculosis (right apex).	Conj.	0.5.....	+	24	+.....	None	Neg.....	None.....	+	
				Scar. { Human	.....	+	48	+ (10x7).....	"	"	"	+	
				Scar. { Bovine	.....	+	48	+ (8x8).....	.....	"			
				Oint.	.....	+	96	+++ (100)..	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	"	"	"		
6	C. R. ...	5	Suspicious pulmonary tuberculosis (right apex).	Conj.....	0.75.....	+	26	+++.....	Photophobia	Neg.....	None.....	+	
									Pain in eye				
				Scar.	....	+	22	++ (25x15)..	None	"	"	—	
				Oint.	.....	+	46	+ (10).....	"	"	"	—	
				S. Cut.....	.....	+	....	++.....	Pain locally.....	"	"		
7	N. McF..	5	Suspicious pulmonary tuberculosis (right apex).	Conj.....	0.5.....	+	24	++.....	None	Neg.....	None.....	+	
				Scar.	.....	+	21	++ (15x15)..	"	"	"	—	
				Oint	.....	+	48	+ (5).....	"	"	"	—	
				S. Cut.....	.....	+	....	+.....	"	"	"		
8	K. W....	5	Suspicious pulmonary tuberculosis (left base).	Conj	0.5.....	+	22	+.....	None	Neg.....	None.....	—	
				Scar. { Human	.....	+	27	+ (4x4).....	"	"	"	—	
				Scar. { Bovine	....	+	27	+ (5x5).....	.....	"	"	+	
				Oint.	.....	+	96	++ (25).....	"	"	"		
				S. Cut.....	.....	+	....	+.....	"				

9	S. K.....	4½	Palpable mesenteric glands.	Conj.....	0.75	—	....	—					
				Scar.....	.....	—	....	—					
				Oint.....	.....	—	....	—					
				S. Cut.....	.....	—	....	—	.....	.....	.....	.....	
10	S. K.....	5	Suspicious pulmonary tuberculosis (right apex).	Conj.....	0.75..	+	28	++.....	None	Neg.....	None.....	+	Positive local reaction.
				Scar.....	.....	+	22	++ (15x10)..	"	"	"	—	
				Oint.....	.....	+	22	+ (6)...	"	"	"	—	
				S. Cut.....	.....	+	....	+.....	"	"			
11	K. K.. ♂	3	Doubtful pulmonary tuberculosis (right apex).	Conj.....	0.5.....	+	30	+.....	None	Neg.....	None.....	—	
				Scar.....	.....	+	24	+ (5x8).....	"	"	"	—	
				Oint.....	.....	+	24	+ (4).....	"	"	"	—	
				S. Cut.....	.....	+	....	+..... ...	.....	.....	.....	.....	
12	H. D.....	3	Palpable mesenteric glands	Conj.....	0.5.....	—	....	—.....	.....	.....	.....	.....	5 days after test applied rt. eye "flared up" suggesting a reaction; 3 days later O. S. was affected. Boy had purulent conjunctivitis.
				Scar.....	.....	—	....	—					
				Oint.....	.....	—	....	—					
				S. Cut.....	.....	—	....	—					
13	J. M	3	Palpable mesenteric glands.	Conj.....	0.5.....	—	....	—					
				Scar..	.....	—	....	—					
				Oint.....	.....	—	....	—					
				S. Cut.....	.....	—	....	—					
14	J. K.....	6	Palpable mesenteric glands.	Conj.....	0.5	+	28	+.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	24	+ (5x7).....	"	"	"		
				Oint.....	.....	+	24	++ (25)....	"	"	"	+	
				S. Cut.....	.....	+	....	++.....					
15	M G.....	3	Suspicious pulmonary tuberculosis (right base).	Conj.....	0.5...	+	32	++.....	None	Neg.....	None.....	++	
				Scar.....	.....	+	24	++ (10x10)..	"	"	"	++	
				Oint.....	.....	+	24	+ (4).....	"	"	"	++	
				S. Cut.....	.....	+	....	+.....	"	"	"		
16	C. C.....	6	Suspicious pulmonary tuberculosis (right apex).	Conj.....	1st dose 0.5 2nd " 0.75	+	24	+.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	24	+ (10x10)....	"	"	"	+	
				Oint.....	.....	+	24	+.....	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	"	"	"		
17	J. C.....	3	Palpable mesenteric glands.	Conj	1st dose 0.5 2nd " 0.75	+	24	+.....	Photophobia....	Neg.....	None.....	*	*Child was taken home before return reaction could be observed.
				Scar.....	.....	+	24	+ (8x10).....	None	"	"		
				Oint.....	.....	+	24	+ (1).....	"	"	"		
				S. Cut.....	.....	+	....	+.....	"				
18	G. M....	4	Cervical adenitis (tuberculous?)	Conj.....	0.5.....	+	28	+++.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	41	++ (15x15) ..	"	"	"	+	
				Oint.....	.....	+	41	+++ (50)...	"	3 papules.....	"	+	
				S. Cut.....	.....	+	....	++.....	"				
19	M. C.....	6	Palpable mesenteric glands.	Conj.....	1st dose 0.5 2nd " 0.75	+	24	+.....	None	Neg.....	None.....	—	
				Scar.....	.....	+	23	+.....	"	"	"	—	
				Oint.....	.....	+	76	+ (14)	"	3 papules.....	"	+	
				S. Cut.....	.....	+	....	+.....	"		"		

II (Concluded). CASES IN WHICH THERE WERE PHYSICAL SIGNS SUGGESTING TUBERCULOSIS.

Case.	Name.	Age.	Suspected Tuberculosis.	Test Applied.	Dose. Per cent.	Pos. Neg.	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction	Remarks.
20	M. C.....	4	Suspicious tuberculous pleurisy (l. base).	Conj.....	0.5.....	+	24	+.....	None	Neg.....	None.....	+	
				Scar.....	.....	+	72	+ (9x13).....	"	"	"	+	
				Oint.....	.....	+	70	+ (12).....	Itching.....	2 papules.....	"	+	
				S. Cut.....	.....	+	....	++					
21	A. L.....	4	Suspicious pulmonary tuberculosis (r. apex)	Conj.....	0.75.....	—	....	—					
				Scar.....	.....	—	....	—					
				Oint.....	.....	—	....	—					
				S. Cut.....	.....	—	....	—					
22	E. F.....	4½	Palpable mesenteric glands.	Conj.....	0.75.....	+	24	+++.....	None.....	Neg.....	None.....	+	
				Scar.....	.....	+	24	++ (20x15)..	"	"	"	+	
				Oint.....	.....	+	24	+++ (250+)	"	"	"	—	
				S. Cut.....	.....	+	....	+	"				
23	M. M....	7	Tuberculous pleurisy?	Conj.....	0.75.....	+	24	++.....	None.....	Slight redness in 48 hours.	None.....	+	
				Scar.....	.....	+	24	+++ (25x30)	"	1 papule.....	"	+	
				Oint.....	.....	+	48	+ (17).....	"	.....	Much enlarged inguinal gland.	+	
				S. Cut.....	.....	+	....	+	"				
24	B. D.....	8	Suspicious pulmonary tuberculosis (r. apex)	Conj.....	0.5.....	+	24	+++.....	Photophobia....	Neg.....	Phlyct. conjunctivitis.	+	Note that Bovine Scar. was more marked than human.
				Scar. { Human	.....	+	48	++ (16x16)..	None.....	"	None.....	+	
				Scar. { Bovine	.....	+	72	+++ (20x20)	.....	"	"	+	
				Oint.....	.....	+	72	++ (35) ...	"	"	"	+	
25	T. McF..	7	Suspicious pulmonary tuberculosis.	Conj.....	0.5.....	+	48	+++.....	Chimosis, photophobia.	Neg.....	None.....	+++	Most marked reaction of any case.
				Scar. { Human	.....	+	48	+++ (20x20)	.....	"	"	+++	
				Scar. { Bovine	.....	+	24	+ (9x9).....					
				Oint.....	.....	+	72	+++ (200+)	Itching.....	"	"	+++	
				S. Cut.....	.....	+	....	++.....					
26	G. D.....	6	Suspicious pulmonary tuberculosis (r. apex)	Conj.....	0.5.....	—	....	—.....	None.....	Neg.....	None.....	—	
				Scar. { Human	.....	+	96	+ (6x6).....	"	"	"	+	
				Scar. { Bovine	.....	—	....	—.....	"	"	"	—	
				Oint.....	.....	+	72	++ (25).....	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	"				
27	M. J.....	3½	Lobar pneumonia and meningitis, probably tuberculous.	Conj.....	1.....	—	....	—.....	.....	.....	.....	.....	Died 5 days after test; illness 3 wks.; fever 2 wks.; none last wk. of life.
28	H. G.....	8	Chorea and acute endocarditis; signs suggesting quiescent lesion of right apex.	Conj.....	1.....	+	48	+++.....	Photophobia, pain in eye	Neg.....	None	.....	2 eye tests: 1st 1⅛, 2d 5⅛, other eye. First +++, Second ++. Return reaction in other eye.
				Scar.....	.....	+	24	++ (12x12)..	None.....	"	"		
				Oint.....	.....	—	....	—..					

The changes produced in the conjunctival sac by the first instillation are generally tuberculous tissue changes; hence the second and third instillations into the conjunctival sac produce a violent reaction, which is in accord with the fundamental discovery of Koch that tuberculin produces inflammation in tuberculous alterations. If the phenomena in the eye were due to a purely fluid poison, it would be hard to understand why the ability to react which is produced by the first instillation should persist for months, and also why this ability to react does not extend to the eye as a whole, in view of the rapidity with which fluid diffusible substances introduced into the conjunctiva make their way into the eye.

The theory of Wolff-Eisner that the efficacy of tuberculin injections and inoculations depends on the presence of the bodies of dead bacteria in the tuberculin—in other words, that it is a bacteriolytic reaction—is in accord with these views.

Bandler and Kreibisch also studied the late papules histologically and observed infiltration with mononuclear cells and some epithelioid cells and giant cells or what they termed the beginnings of giant cells, which, however, differed from the Langhans type. These findings are interesting and stimulated us to make histologic studies of the papules from the delayed abdominal reaction, above referred to. For the sake of comparison, we studied with this a papule from a normal reaction. The sections were kindly made and reported on by Dr. C. Y. White, and confirmed by Dr. M. B. Hartzell. They agreed that neither lesion differed in any way from the ordinary histologic picture of simple inflammation of the skin.

CONFIRMATION BY THE SUBCUTANEOUS TEST.

In eighty-five cases we applied the subcutaneous test in confirmation of the other tests. Sixty-three of these had been positive to the superficial tests and twenty-two negative. The subcutaneous test verified all the negative cases, by showing no evidence of reaction. In two of the positive cases, this confirmation was lacking, and in one case doubtful.

The injections were given in the lower right or left lumbar region. When it was necessary to repeat the dose, it was given on the opposite side.

In the first group of nine cases, including negative cases and mild reactions, the dosage was 0.1 mg. The only evidence of reaction occurred in the mild cases, and this was definite enough to leave no question as to the nature of the reaction.

In the second group we gave 0.1 mg. subcutaneously and, after forty-eight hours, repeated the test in the doubtful cases, giving 0.5 mg.

In the third group of somewhat older children we gave 0.5 mg., as the initial dose, in the doubtful cases, repeating with 1 mg.

In the last group we gave 0.75 mg. as an initial dose and found it unnecessary to repeat the injection in any. We observed no severe reactions. In one case there was vomiting about fourteen hours after the injection and in another enlargement of the inguinal glands associated with tenderness and some lymphangitis.

RETURN REACTIONS.

We observed very striking return reactions in all but 16 per cent. of the cases, 67 per cent. of the total number showing return conjunctival reactions, 65.5 per cent. return cutaneous reactions and 59 per cent. return ointment reactions. There were no evidences of inflammatory reaction in any of the tuberculin areas in the cases, which had been negative to the original tests. The most striking return reactions were those occurring on the abdomen over the area to which the ointment had been applied (Fig. 9). This so-called return reaction, as it appears after the cutaneous and ointment reactions, does not possess the characteristics of the original reaction. It is merely a mottled, pinkish blotching of the regions which had been occupied by the original reaction and shows neither elevation, papulation nor induration. The difference is very clearly shown by a comparison of the sketches showing the original and return abdominal reactions.

We observed no return reactions following the application of the superficial tests in the cases in which they were made at intervals. In several cases in which a second eye test was made in the original control eye there was a slight reaction in the opposite eye (original test eye). In this connection it may be pointed out that, in a few instances, we observed a bilateral conjunctival reaction after the instillation in one eye, a point which has been commented on quite frequently by other investigators and which has been explained most commonly on the basis of a transmission of the tuberculin from one eye to the other, by rubbing first the instilled and then the control eye.

POSTMORTEM CONFIRMATION.

In the few instances in which we were able to obtain autopsies the postmortem findings confirmed the results of the tests applied. Where the reactions were negative the autopsies failed to reveal any evidences of tuberculosis. In one case in which only the conjunctival test was applied with a positive reaction, some cervical glands removed surgically were proved tuberculous by the histologic examination, and in another

case reacting to the conjunctival test, miliary tuberculosis, tuberculous meningitis and enlarged tuberculous mesenteric glands were found at the autopsy.

There has been a considerable amount of postmortem study of cases in which the conjunctival and cutaneous tests have been applied. Von Pirquet made autopsies on one hundred children whom he had tested subcutaneously. Fifty-two of these, in whom the scarification test had been negative, showed no tuberculous changes macroscopically. Thirty-four of his patients died of tuberculosis, diagnosed clinically. Thirteen of these had been tested during the last ten days of life and none of them had reacted. Thirteen patients, dying of non-tuberculous conditions, had shown tuberculosis as an accessory finding. In this latter group nine had reacted positively, while in four, of whom three were not examined within the last ten days of life, the test was negative, and in one case, which had reacted, no macroscopic evidences of tuberculosis were found at autopsy.

Blum, Comby, Morelli, Wolff-Eisner, Letuelle, Prouff, A. Marie, Raviart, Otto Grunbaum, Hischler, Eyre, Wedd and Herz, Feer and Gaupp made autopsies in a large number of cases (more than sixty) in which either the conjunctival or scarification tests had been applied and, without exception, confirmed both their positive and negative findings. On the other hand, Bourget quotes two cases, one of hemiplegia and one of acute peritonitis; Massary and Weil a case of carcinoma; Bourget and Stilling a case of typhoid fever; Cohn and Simonin each a similar case, in which they obtained positive conjunctival reactions and failed to find evidences of tuberculosis at the autopsy.

It will be seen from the foregoing that the results of postmortem investigation have, in the main, confirmed the specificity of these reactions. The value of the negative results, as Soques has pointed out, may always be questioned, unless thorough macroscopic, microscopic and bacteriologic examinations, and animal injections of the tissues have been made.

When we realize that any of these tests will reveal the most minute foci of tuberculosis, it is very easy to understand how readily the lesions may be overlooked in the course of an ordinary autopsy.

When tuberculous lesions are found at the autopsy in cases which have not reacted, the relationship between the time of reaction and the date of death must be taken into consideration, because it is the rule that tuberculous cases fail to react during the last days of life, as well as under certain other conditions.

III. CASES WHICH WERE DEFINITELY TUBERCULOUS.

Case.	Name.	Age.	Tuberculous.	Test Applied.	Dose. Per cent.	Pos. + Neg. −	Maximum Reaction. Hours.	Type.	Subjective Symptoms.	Control.	Complications.	Return Reaction.	Remarks.
1	L. L.....	4	Advanced pul. tub. with cavity formation, pertussis.	Conj.....	0.5.....	+	24	+.....	None.....	Neg.....	None.		
				Scar.....	.....	+	24	+ (4x4).....	"	"	"		
				Oint.....	.....	+	48	+ (1).....	"	"	"		
2	A.S.(Col)	6	Lobar pneu. tub. (r. apex.)	Scar.....	.....	+	24	+ (10x10)....	None.....	Neg.....	None.		
				Oint.....	.....	−	....	−.....					
3	J. H.....	3	Tuberculous bronchopneumonia.	Conj.....	0.75.....	+	24	+.....	None.....	Neg.....	None.	.....	Tests applied 6 and 7 days before death. Fever fluctuating between 100° and 105°. All reactions very mild. Mother died of tuberculosis.
				Scar.....	.....	+	24	+.....	"	"	"		
				Oint.....	.....	+	24	+.....	.....	"			
4	E. S.....	4	Tub. dactylitis, tub. bronchial glands.	Conj.....	0.5.....	+	24	+.....	Photophobia....	Neg.....	None.	.....	Father died of tuberculous.
				Scar.....	.....	+	48	+ (7x7).....	None.....	"	"		
				Oint.....	.....	+	48	++.....	"	"	"		
5	J.R.(Col)	6	Pulmonary tuberculosis..	Conj.....	0.5.....	+	24	++.....	None.....	Neg.....	None.		
				Scar.....	.....	+	24	++ (15x15)..	"	"	"		
				Oint.....	.....	−	....	−.....					
6	E. W.....	8	Tub. cervical adenitis and pul. tuberculosis.	Conj	1.....	+	25	+.....	None.....	Neg.....	None.	.....	Glands removed surgically showed tuberculosis.
7	L. F.....	3	Tub. meningitis, miliary tubercles in spleen, tub. of mesenteric glands.	Conj..	0.5	+	11½	+...	None.....	Neg.....	None.	.....	Eye instilled 48 hrs. before death.
8	S. F.....	9	Tub. of tonsils and bronch. glands x-ray confirmation.	Conj.....	0.5.....	+	....	+.....	None.....	Neg.....	None.		
9	W. M.....	5	Old Pott's disease.	Conj.....	0.5.....	+	24	++.....	None.....	Neg.....	None.		
				Scar.....	.....	+	48	+.....	"	"	"		
10	S. S.....	6	Tuberculous arthritis, knee.	Conj.....	0.5.....	+	24	+.....	None.....	Neg.....	None..	+	
				Scar.....	.....	+	48	++ (10x20)..	"	"	"	++	
				Oint.....	.....	+	24	+++ (250 .)	"	"	"	+	
				S. Cut.....	.....	+	....	+.....	Pain in knee and abdomen.				
11	A. B.....	10	Tuberculous peritonitis.	Conj.....	0.5...;	+	24	+.....	None.....	Neg.....	None..	—	
				Scar.....	....	—	....	−.....	"	"	"	—	
				Oint.....	.....	—	....	−.....	"	"	"	—	
				S. Cut.....	.....	—	....	−.....	"	"	"	.....	Slight loc. reaction.
12	W. O'B..	9	Advanced pulmonary tuberculosis; entire r. lung and upper lobe l. lung.	Conj.....	0.5.....	—	....	−.....	.....	.....	.....	.....	Child died 9 days after tests were applied.
				Scar.....	.....	—	....	−..... .					
				Oint	.....	—	....	−.....					
				S. Cut.....	.....	—	....	−.....					

13	J. S.....	5	Pulmonary tub. chronic; r. upper lobe.	Conj.....	0.5.....	+	24	+.....	None.....	Neg.....	None.....	+		
				Scar.....	.....	+	24	+ (7x8).....	"	"	"	+		
				Oint.....	.....	+	72	+ (13).....	"	"	"	—		No fever, only local reaction.
				S. Cut.....	.....	+	....	+ ?.....	"	"	.....	.....		
14	A. D.....	7	Pulmonary tub. (r. apex), tub. mesenteric glands.	Conj.....	1st dose 0.5 2nd " 0.75	+	30	+.....	None.....	Neg.....	None.....	+		Right eye tested .5% sol. negative. Left eye 6 days later 1% sol. positive.
				Scar.....	.....	+	24	++ (10x12)..	"	"	"	+		
				Oint.....	.....	+	24	+ (15).....	"	"	"	+		
				S. Cut.....	.....	+	..	+.....	"	"	"			
15	P. C.....	4	Glandular tuberculosis.	Conj.....	0.5.....	+	28	++.....	None	Neg.....	None.			
				Scar.....	.....	+	25	+ (10x10)....	"	"	"			
				Oint.....	.....	+	22	+ (5).....	"	1 papule.....	"			
16	G. B.....	4	Pulmonary tub. (r. apex.)	Conj.....	0.5.....	+	23	+.....	None.	Neg.....	None.			
				Scar.....	0.75.....	—	....	—.....	"	"	"			
				Oint.....	.....	+	52	++ (26).....	"	"	"			
17	J. B.....	3	Glandular tuberculosis.	Conj.....	0.5.....	+	48	++.....	None.....	Neg.....	Phlyct. conjunc. 8 days after.			
				Scar.....	.....	+	24	++ (18x13)..	"	"	None.			
				Oint.....	.....	+	48	+++ (80)...	"	"	"			
18	K. L.....	4	Tub. adenitis (cervical).	Conj.....	0.5.....	+	48	+.....	None.....	Neg.....	Phlyct. conjunc. 8 days after test.	.....		Improvement and recurrence.
				Scar.....	.....	+	48	++ (25x12)..	"	"	None.			
				Oint.....	.....	+	48	+ (1).....	"	"	"			
19	A. C.....	4	Pulmonary tub. (r. apex.)	Conj.....	1st dose 0.5 2nd " 0.75	+	23	+.....	None.....	Neg.....	None.....	+++		
				Scar.....	.....	+	48	++ (10x10)..	"	"	"	++		
				Oint.....	.....	+	48	+++ (60)...	Itching.....	Many papules.	"	++		
				S. Cut.....	.....	+	....	+.....	"	"	"			
20	D. D.....	4	Pulmonary tub. (r. apex.)	Conj.....	1st dose 0.5 2nd " 0.75	+	17	++.....	Photophobia...	Neg.....	None.....	—		
				Scar.....	.....	+	30	+++ (25x20)	None.....	"	"	+		
				Oint.....	.....	+	39	++ (25).....	"	2 papules.....	"	+		
				S. Cut.....	.....	+	48	+++.....	"					
21	T. M.....	3	Pulmonary tub. (r. apex.)	Conj.....	1st dose .05 2nd " 0.75	+	24	+.....	None	Neg.....	None.....	—		
				Scar.....	.....	+	24	+.....	"	"	"	—		
			Adenitis.....	Oint.....	.....	+	24	+.....	"	"	"	—		
				S. Cut.....	.....	+	46	+.....	"	"	"			
22	L. M.....	7	Pulmonary tub. and tuberculous arthritis of r. elbow joint.	Conj.....	0.75.....	+	24	++.....	None	Neg.....	None	.....		Abdominal reaction continued at maximum for 3 weeks; had not disappeared entirely at end of 4 weeks.
				Scar	.....	+	48	++ (10x15)..	"	"	"			
				Oint.....	.....	+	48	+++ (100+)	"	"	"			

For instance, in one of our cases of advanced pulmonary tuberculosis, the patient being cachectic and emaciated, we obtained negative results to all three of the superficial tests, as well as to the subcutaneous. In the experience of those who have used these tests, negative results have been almost universal in cases of this type.

Dufour states that since 1899 he has had uniformly negative results to the subcutaneous test in cachectic cases, in individuals attacked with acute, fatal tuberculosis, and in practically all tuberculous cases during the last few days of life. With the newer tests, the results have been the same. This phenomenon is explained on the basis that the organism is so overwhelmed by the poisons of tuberculin, that it loses its power to react, or, as Baldwin expresses it, there occurs an exhaustion of the reactive mechanism by the excessive absorption of poison. Von Pirquet makes the suggestion, on the basis of some of his results, that the absence of reaction during the last days of life may be only relative and can be overcome by very large doses of the poison.

It not infrequently happens that individuals who fail to react to the first test will react when the test is repeated. This has been interpreted to mean that such individuals are the bearers of latent foci and, as their tissues have not been in contact with the poisons of the tubercle bacillus for a long time, the first application of the tuberculin merely stimulates immunization, thus paving the way for the occurrence of a reaction to the second test.

This question is closely related to the sensitizing of the tissues, in regard to which there must exist a great diversity of opinion until added knowledge makes it possible for us to arrive at more definite conclusions. Von Pirquet admits the possibility of inoculation producing immunity, but inclines, from his experiences in the inoculation of tuberculin, to believe that it is not followed by hypersensitiveness.

The latter view is maintained by Wolff-Eisner, Calmette and many others, and certainly the histologic findings of Daels previously referred to would seem to require some explanation in this connection.

This question of anaphylaxis will necessarily throw some doubt on the absolute specificity of the tuberculin test, if it is proved that it is entirely possible to produce a condition of hypersensitiveness in the use of tuberculin. On the other hand, the weight of experience, the enormous percentage of postmortem confirmations of the subcutaneous tests in animals, and of the superficial tests in human beings and the almost uniform confirmation of the superficial test by the subcutaneous method, would seem to suggest that the tests can be relied on to indicate the existence of tuberculosis in human beings, except in the type of cases

which has been previously referred to. Admitting this, the value of these tests, from the standpoint of diagnosis, would be absolute as to the existence of some form of tuberculosis, but the fact that they reveal the most minute and even the inactive and possibly healed forms of the disease, together with their failure to react in the presence of associated cachexia and in the advanced stages of the disease and especially in the most acute forms of tuberculosis, make them of much less value than we had hoped they might be in the differential diagnosis between the irregular types of tuberculosis and other conditions which simulate them.

Krause, Liesenberger and Russ, as well as Cohn, obtained a large percentage of positive results with the conjunctival test in cases of typhoid fever and also obtained positive results in tuberculous cases by the instillation of typhoid toxin, from which they argue that the test is not specific and that reactions are simply an expression of a hypersensitiveness of the organism to toxins in general. One of Cohn's cases came to autopsy and showed no evidences of tuberculosis. Bourget and Stilling also report a positive conjunctival test in a case of typhoid fever which showed no lesions of tuberculosis at the autopsy. These results have not, however, been confirmed by the observation of others. In our series, the test was applied to three cases of typhoid fever, both during the febrile period and in convalescence. In two cases, the result was negative, while in the other it was positive at both periods of the disease.

Austin and Grünbaum, Leroux, Trannoy, Hutchings, Lesne and Marré, Olmer and Terras, Levy and Wolff-Eisner report negative results in nineteen cases of typhoid fever. The negative results in cases of typhoid fever just quoted would seem to disprove the theory of the authors first mentioned and negative the value of their findings, as bearing on the specificity or diagnostic value of the tests.

It would seem to us that the negative results are probably of more value than the positive findings in differential diagnosis, except in serious febrile conditions. They definitely eliminate the possibility of tuberculosis.

We believe that the test will prove of value in its positive results in making it possible to separate the infected from the non-infected in institutions in the early recognition of infection and the consequent early adoption of treatment in the determination of the beginning of the infection, especially in tuberculous families, and possibly in connection with the determination of the origin of certain cases or groups of cases, as well as in stimulating us to a more careful study of the methods of transmission of the disease. The observations of Rosenberger regarding the frequency of tubercle bacilli in the stools, even in cases not clinically

tuberculous, as well as the recognition of the tubercle bacilli in the urine, suggest the possibility of a more frequent transmission of contagion through the medium of the discharges than we have been inclined to believe. This would seem to be an especially probable mode of transmission in the large overcrowded institutions, in which the soiled body and bed linens are washed either infrequently or inadequately. In an institution, for instance, such as that from which the majority of our cases have been drawn, it would seem unlikely that the number of actively tuberculous cases, especially of pulmonary cases, would be sufficient to account for the widespread dissemination of infection which exists there, and, unless we assume that these children are infected either prior to admission or that they are infected through the medium of the milk which is supplied them, we must conclude that there is some other manner of transmission of the disease.

There has been some effort made to place a prognostic significance on the type of reaction, especially on the type of the cutaneous reaction. It would seem possible that a gradual diminution of reaction in the advanced cases may indicate an unfavorable course.

COMPARISON OF HUMAN AND BOVINE SCARIFICATION TESTS.

Suggested by the differential tuberculin reaction of Detre, by which he attempts to differentiate between the bovine and human type of infection by the differences in reaction to filtrates of the human and bovine bacilli, we applied, by the scarification method, 10 per cent. solutions of tuberculin original—prepared, the one from bovine, the other from human cultures—in the same individual. The upper arm was chosen for the application and the tests were applied in twenty-four cases. The results showed the reaction to the human tuberculin the stronger in eleven cases, two of these which reacted strongly not reacting at all to the bovine. The degree of reaction was the same in eight cases and in two it was much stronger to the bovine than to the human, while in three there was no reaction to either. Generally speaking, the differences in degree of reaction where the one was stronger than the other were very striking. While these figures are of no value for purposes of deduction, they are nevertheless somewhat suggestive.

ANIMAL EXPERIMENTS.

In the hope that we might be able to throw some light on certain interesting features of this question, we undertook some experimental work on rabbits.

What we aimed to accomplish was to determine whether the type of the reaction bore any relationship to the stage of the disease or the nature or location of the lesion. Incidentally, we endeavored to create immunity in several normal rabbits by the intraperitoneal injection of tubercle toxin and to sensitize the conjunctival tissues in two normal rabbits and one tuberculous rabbit, which had shown no tendency to react, by the repeated instillation of tuberculin precipitate.

For some reason, which, up to the present, we have been unable to explain, our results were entirely negative. In the case of the attempts to induce immunity this may not be surprising, but our failure to obtain reactions in definitely tuberculous animals—proved by autopsy—the result is, to say the least, confusing.

We were at first inclined to believe that the inoculation with a bovine culture and the use of tuberculin of human origin might have some bearing on the result; but we note that Calmette, Breton and Petit obtained positive reactions in rabbits under similar conditions, from which we assume that this explanation is not satisfactory. We then incriminated the dosage, feeling that we might have overwhelmed the animals with so much toxin that immunity was not established. When we came to post our animals, we found that intravenous rabbit No. 4, killed on the fifty-first day, showed little beyond a lesion at the point of injection. We felt that this accusation would not hold for this case. When we found that one of our control rabbits which had had its eye instilled on the fifth of April (normal rabbit No. 1), and was killed on the sixth of May, showed a few tubercles in the left lung, we were still further convinced that the dose was not responsible for our negative results. We must, however, consider the possibility of infection in this case between the date of the last reaction (April 5) and the time of the autopsy (May 6).

In the light of the fact that the authors mentioned, together with Nobécourt and Montoux, Vallée, Lingnières, Naegeli, Akerblom and Venier and Gilliland (the last-named working with the same tuberculin which we used and in the same dosage), have obtained positive eye reactions after infecting their rabbits with both types of organisms, with varying doses, many of them larger than ours, and by the various methods, we feel that our negative findings, while failing to accomplish the purposes we had in view, have nevertheless presented a new problem which we hope to solve by further investigation.

The tuberculin which we used in testing these animals was of the same lot that we used successfully in human beings, both before and

after these experiments were done. The variability of the results of the authors referred to may bear some relationship to our uniform negative results.

LABORATORY REPORT ON THE ANIMAL EXPERIMENTS.

Culture Used for Inoculation.—Culture H of the laboratory of the State Live Stock Sanitary Board. It is a virulent bovine culture, and has been growing on artificial media since about 1902.

Preparation of Emulsion.—The emulsion was made from a six weeks old bouillon culture and in such strength that 1 c.c. of emulsion represented 0.001 gm. of dry tubercle bacilli.

Animals Used.—Seventeen rabbits were used in these experiments; twelve were inoculated with the above emulsion; four intraperitoneally with 0.5 c.c. (herein referred to as intraperitoneal rabbits 1, 2, 3 and 4); subcutaneously with 1 c.c. (subcutaneous rabbits 1, 2, 3 and 4); four intravenously with 0.25 c.c. (intravenous rabbits 1, 2, 3 and 4); two received subcutaneous injections of tuberculous toxin (filtrate from six weeks old culture) (toxin rabbits 1 and 2); three were not inoculated (normal rabbits 1, 2 and 3).

Tuberculin precipitate is indicated in the following tables by "T. P.":

CONJUNCTIVAL TUBERCULIN REACTION EXPERIMENTS ON KNOWN TUBERCULOUS RABBITS.

TABLE OF RESULTS.

Date.	Day.	No. of Rabbits, Instillation, etc.	18 hrs.	24 hrs.	48 hrs.
		Intraperitoneal Rabbit 1.			
Feb.					
26	1	Inoculated four rabbits intraperitoneally	....	....	....
28	3	Instilled left eye 0.5 per cent. T. P.	Neg.	Neg.	Neg.
March.					
2	6	Instilled right eye 0.5 per cent. T. P.	Neg.	Neg.	*....
5	9	Autopsy; see below.			
		Intraperitoneal Rabbit 2.			
5	9	Instilled left eye 0.5 per cent. T. P.	Neg.	Neg.	Neg.
10	14	Instilled right eye 0.5 per cent. T. P	†....	....	Neg.
12	16	Autopsy; see below.			
		Intraperitoneal Rabbit 3.			
17	21	Instilled left eye 0.5 per cent. T. P.	....	‡....	Neg.
18	22	Instilled right eye 0.5 per cent. T. P.	....	‡....	‡....
20	24	Autopsy; see below.			
		Intraperitoneal Rabbit 4.			
30	34	Instilled left eye 0.75 per cent. T. P.	....	‡....	Neg.
April.					
8	43	Instilled right eye 1 per cent. T. P.	Neg.	Neg.	Neg.
16	51	Died. Autopsy; see below.			
March.					
2	1	Inoculated four rabbits subcutaneously.			
		Subcutaneous Rabbit 1.			
9	7	Instilled left eye 0.5 per cent. T. P.	Neg.	Neg.	Neg.
23	21	Instilled right eye 0.5 per cent. T. P. Abscess at seat of inoculation at this date.	Neg.	Neg.	Neg.

Date.	Day.	No. of Rabbits, Instillation, etc.	18 hrs.	24 hrs.	48 hrs.
		Subcutaneous Rabbit 2.			
April.					
2	31	Instilled left eye 1 per cent. T. P.	Neg.	Neg.	Neg.
		Abscess discharging at this date.			
14	43	Instilled right eye 1 per cent. T. P.	Neg.	Neg.	Neg.
		Subcutaneous Rabbit 3.			
30	59	Instilled left eye 0.75 per cent. T. P.	Neg.	Neg.	Neg.
		Subcutaneous Rabbit 4.			
30	59	Instilled left eye 0.75 per cent. T. P.	Neg.	Neg.	Neg.
May.					
5	64	Autopsies done on all subcutaneous rabbits; see below.			
March.					
13	1	Inoculated four rabbits intrathoracically.			
		Intrathoracic Rabbit 1.			
17	5	Instilled left eye 0.5 per cent. T. P.	Neg.	Neg.	Neg.
23	11	Instilled right eye 0.75 per cent. T. P.	Neg.	Neg.	Neg.
25	13	Autopsy; see below.			
		Intrathoracic Rabbit 2.			
30	18	Instilled left eye 0.75 per cent. T. P.	....	‡....	Neg.
Apr.					
14	33	Instilled right eye 1 per cent. T. P.	Neg.	Neg.	Neg.
16	35	Autopsy; see below.			
		Intrathoracic Rabbit 3.			
8	27	Died. Autopsy; see below.			
		Intrathoracic Rabbit 4.			
May.					
1	50	Instilled left eye 0.3 per cent. T. P.	Neg.	Neg.	Neg.
5	54	Autopsy; see below.			
		Inoculated four rabbits intravenously, March 16.			
		Intravenous Rabbit 1.			
March.					
20	5	Instilled left eye 0.75 per cent. T. P.	Neg.	Neg.	Neg.
24	9	Instilled right eye 0.75 per cent. T. P.	Neg.	Neg.	Neg.
26	11	Autopsy; see below.			
		Intravenous Rabbit 2.			
30	15	Instilled left eye 1 per cent. T. P.	Neg.	Neg.	Neg.
April.					
16	16	Instilled right eye 0.3 per cent. T. P.	Neg.	Neg.	Neg.
12	28	Autopsy; see below.			
		Intravenous Rabbit 3.			
14	30	Died before test was applied. Autopsy; see below.			

Date.	Day.	No. of Rabbits, Instillation, etc.	18 hrs.	24 hrs.	48 hrs.
		Intravaneous Rabbit 4.			
30	46	Instilled left eye 0.3 per cent. T. P.	Neg.	Neg.	Neg.
May.					
3	51	Autopsy; see below.			

*A very faint injection of the vessels which we considered negative. It did not develop until 48 hours.

†An injection very slightly more marked than Note 1. Since this is the only rabbit in which we obtained this result, we considered it negative.

‡A milky discharge from the inner canthus. Not pus; unaccompanied by any injection of the vessels. Negative.

VON PIRQUET (SCARIFICATION) AND MORO (OINTMENT) TEST EXPERIMENTS.*

Date.	Day of		——Results——	
May	Disease.	No. of Rabbit, Test, etc.	24 hrs.	48 hrs.
2	..	*Normal Rabbit 2.* Sacrification test.	Neg.	Neg.
April.				
2	..	Ointment test.	Neg.	Neg.
		Normal Rabbit 3.		
2	..	Scarification test.	Neg.	Neg.
2	..	Ointment test.	Neg.	Neg.
		Toxin Rabbit 1.		
2	24	Scarification test.	Neg.	Neg.
2	24	Ointment test.	Neg.	Neg.
		Toxin Rabbit 2.		
2	24	Scarification test.	Neg.	Neg.
2	24	Ointment test.	Neg.	Neg.
		Intrathoracic Rabbit 4.		
2	51	Scarification test.	Neg.	Neg.
2	51	Ointment test.	Neg.	Neg.
		Intravenous Rabbit 4.		
2	48	Scarification test.	Neg.	Neg.
2	48	Ointment test.	Neg.	Neg.
		Subcutaneous Rabbit 1.		
2	61	Scarification test.	Neg.	Neg.
2	61	Ointment test.	Neg.	Neg.
		Subcutaneous Rabbit 2.		
2	61	Scarification test.	Neg.	Neg.
2	61	Ointment test.	Neg.	Neg.

*Scarification test sol. 20 per cent. Koch's old tuberculin. Ointment test sol. equal parts tuberculin original and lanolin (anhydrous).

EXPERIMENTS

To Determine Whether the Conjunctival Tissues Can Be Sensitized by the Instillation of Tuberculin Precipitate; Whether This Results from Frequently Repeated Instillations or from Instillations Made at Longer Intervals; and the Time Required to Sensitize.

Three rabbits were used; two normal (Normal No. 1 and Normal No. 2) one tuberculous (subcutaneous No. 1).

Date.	Day.	Eye.	No. of Instillation.	Strength of Tuberculin Per Cent.	Result 24 hrs.
		Normal Rabbit 1.			
Feb. 28	1	Left	1	0.5	Neg.
April. 2	35	Left	2	1	Neg.
5	38	Right	1	1	Neg.
		See autopsy.			
		Normal Rabbit 2.			
April. 2	1	Left	1	1	Neg.
3	2	Left	2	1	Neg.
5	4	Left	3	1	*....
6	5	Left	4	1	†....
7	6	Left	5	1	Neg.
8	7	Right	1	1	Neg.
May. 1	30	Right	2	.3	Neg.
		Subcutaneous Rabbit 1.			
March. 9	1	Left	1	0.5	Neg.
25	15	Right	1	.75	Neg.
April. 2	24	Left	2	1	Neg.
3	25	Left	3	1	Neg.
5	27	Left	4	1	‡....
6	28	Left	5	1	Neg.
7	29	Left	6	1	Neg.
8	30	Right	2	1	Neg.
30	52	Left	7	.3	Neg.

*Very slight injection of vessels, a milky fluid from inner canthus and a sticky, granular appearance of conjunctiva.

†Some swelling of conjunctiva at inner canthus; injection of vessels equal in both eyes.

‡A very slight injection of vessels.

EXPERIMENTS

To Determine if the Subcutaneous Injection of Tuberculin will Sensitize the Tissues of the Eye to the Tuberculin Precipitate, and if Eyes Which Had Already Been Instilled Would Show Any Inflammatory Reaction.

Three rabbits were used; Normal rabbit 3, an animal on which no work had been done; Normal rabbit 2, whose eyes had been tested (see sensitizing experiment); Intraperitoneal rabbit 4, whose eyes also had been tested (see conjunctival tuberculin tables).

As shown in the accompanying tables, the temperatures of these rabbits were taken three times a day for three successive days; 0.1 c.c. of Koch's old tuberculin was injected subcutaneously into each rabbit on the fourth day at 8 a. m. and temperatures were taken at 12, noon, and every two hours thereafter until 6 p. m. and again at 8 a. m. of the next day.

Date.	Time.	Normal 3.	Normal 2.	Intraperitoneal.
April.				
9	2 p. m.	101.1	101.0	102.3
9	5 p. m.	100.4	101.2	102.4
10	8 a. m.	99.0	....	103.2
10	12 m.	101.1	101.1	101.3
10	5 p. m.	100.3	100.2	102.4
11	8 a. m.	99.4	100.0	102.3
11	12 m.	100.4	100.0	103.2
11	5 p. m.	102.0	101.0	104.0
12	8 a. m.	1/10 c.c. tuberculin subcutaneously.		
12	12 m.	101.3	100.0	103.4
12	2 p. m.	102.1	101.1	104.2
12	4 p. m.	102.2	100.1	103.4
13	8 a. m.	101.2	100.1	103.2

During the forty-eight hours following the subcutaneous injection of tuberculin in normal rabbit No. 2 and intraperitoneal rabbit No. 4 the conjunctival conditions were watched, but no change occurred. The following table will show, in the case of the first two animals, by how many days the various eye instillations preceded the subcutaneous injection and, in the case of the third animal, the number of days intervening between the subcutaneous injection and the various tests:

TABLE OF RESULTS.

Normal Rabbit 2.

Date.	Day.	Instillation, Etc.	24 hrs.	48 hrs.
April.				
2	11	Instilled left eye, 1 per cent. tuberculin precipitate.	Neg.	Neg.
3	10	Reinstilled left eye, 1 per cent. tuberculin precipitate.	Neg.	Neg.
5	8	Reinstilled left eye, 1 per cent. tuberculin precipitate.	See table.	Neg.
6	7	Reinstilled left eye, 1 per cent. tuberculin precipitate.	See table.	Neg.
7	6	Reinstilled left eye, 1 per cent. tuberculin precipitate.	Neg.	Neg.
8	5	Instilled right eye, 1 per cent. tuberculin precipitate.	Neg.	Neg.
12	1	Subcutaneous tuberculin test. No eye changes occurred.		

Intraperitoneal Rabbit 4.

March.				
30	14	Instilled left 0.75 per cent. tuberculin precipitate.	Neg.	Neg.
April.				
8	5	Instilled right eye 1 per cent. tuberculin precipitate.	Neg.	Neg.
12	1	Subcutaneous tuberculin test. No eye changes occurred.		

Normal Rabbit 3.

12	1	Subcutaneous tuberculin test.		
18	7	Instilled left eye, 1 per cent. tuberculin precipitate.	Neg.	Neg.
30	19	Instilled right eye, 3 per cent. tuberculin precipitate.	Neg.	Neg.
May.				
2	21	Scarification test.	Neg.	Neg.
2	21	Ointment test.	Neg.	Neg.

EXPERIMENTS

To Determine if Tubercle Bacillus Toxin Injected Into Non-tuberculous Rabbits Will Cause These Rabbits to React to the Conjunctival Scarification and Ointment Tests.

Two rabbits, called Toxin Rabbit 1 and 2, each inoculated with 0.1 c.c. of the tubercle toxin intraperitoneally.

Date.	Day.	No. of Rabbit, Instillation, Etc.	24 hrs.	48 hrs.
April.				
9	1	Inoculated 2 rabbits.		
		Toxin Rabbit 1.		
10	2	Instilled left eye, 1 per cent. tuberculin.	Neg.	Neg.
May.				
1	23	Instilled right eye, 0.5 per cent. tuberculin.	Neg.	Neg.
2	24	Scarification test (20 per cent. Koch's old tuberculin).	Neg.	Neg.
2	24	Ointment test (equal parts of tuberculin (T.O.) and anhydrous lanolin).	Neg.	Neg.
6	28	Autopsy; see below.		
		Toxin Rabbit 2.		
April.				
10	2	Instilled left eye, 1 per cent. tuberculin.	Neg.	Neg.
May.				
1	23	Instilled right eye, 0.3 per cent. tuberculin.	Neg.	Neg.
2	24	Scarification test (Koch's old tuberculin).	Neg.	Neg.
2	24	Ointment test.	Neg.	Neg.
6	28	Autopsy; see below.		

AUTOPSIES.

Intraperitoneal Rabbits.

Rabbit 1, March 5, Ninth Day.—Point of inoculation negative. Abdominal cavity: Five or six small tubercles on liver; staining shows tubercle bacilli. Two very small white masses on the mesentery also show tubercle bacilli; spleen, stomach, omentum, kidneys, postperitoneal and mesenteric glands normal. There is an adhesion between the liver and stomach which is not very recent and probably not connected with the tuberculous process. Thoracic cavity normal.

Rabbit 2, March 12, Sixteenth Day.—Point of inoculation shows a small tubercle, staining shows tubercle bacilli. Abdominal cavity: Extensive tuberculosis of the omentum and mesentery. Liver and spleen greatly enlarged and many tubercles scattered throughout the organs. Postperitoneal and mesenteric glands not enlarged; smears from liver, spleen, omentum and mesentery positive for tubercle bacilli. Thoracic cavity normal. An interesting anomaly in this rabbit is a transposition of the abdominal viscera.

Rabbit 3, March 20, Twenty-fourth Day.—Point of inoculation shows a small tubercle in both the skin and peritoneum. Smears positive for tubercle bacilli. Abdominal cavity: Intense injection of omentum and mesentery with small tubercles. Smears positive for tubercle bacilli. Mesenteric glands enlarged and show tubercle bacilli on staining. Spleen normal in size with a very few tubercles. Smears from both organs positive for tubercle bacilli. Thoracic cavity: A few slight pericardial adhesions; smears negative for tubercle bacilli. Lungs and pleura normal; smears negative for tubercle bacilli.

Rabbit 4, April 16, Fifty-first Day.—Rabbit died. Point of inoculation shows a large cheesy tubercle; smears positive for tubercle bacilli. Abdominal cavity: Omentum contracted and massed together by tuberculous adhesions, mesentery and parietal peritoneum contain enormous numbers of tubercles, mesenteric and postperitoneal glands enlarged, liver and spleen attached to stomach by adhesions and studded with tubercles; both are greatly enlarged. Kidneys swollen and congested. Smears from all these organs except the kidneys are positive for tubercle bacilli. Thoracic cavity: A few tubercles throughout the right lung and in the right pleura. Smears positive for tubercle bacilli. Left lung and pleura normal, heart normal, thoracic glands normal.

SUBCUTANEOUS RABBITS.

Rabbit 1, May 5, Sixty-fourth Day.—A large partially broken-down mass at the seat of inoculation. No appreciable enlargement of the subcutaneous glands. Abdominal cavity negative. Thoracic cavity: Both lungs and pleura and pericardium studded with tubercles, smears positive for tubercle bacilli; substernal glands swollen, smears from which show tubercle bacilli; extensive pericardial adhesions.

Rabbit 2.—Abscess which formed at the seat of inoculation discharged, leaving a partially healed ulcer. A chain of enlarged glands runs from this point (the left side midway between the front and rear legs) to the axilla. Axillary glands enlarged. These glands all show tubercle bacilli in smears. Abdominal cavity negative. Thoracic cavity shows a slightly more extensive involvement than in rabbit No. 1 of this series.

Rabbit 3.—A large partially broken-down tuberculous mass at seat of inoculation. No subcutaneous glandular involvement. Abdominal cavity negative. Thoracic cavity: A few tubercles in the lungs, pleura practically free. Pericardium normal; substernal glands enlarged and contain tubercle bacilli.

Rabbit 4.—Cutaneous appearance the same as No. 3 of this series. Abdominal cavity: A few white nodules not suggestive of tubercles on the right kidney; smears negative for tubercle bacilli. Thoracic cavity: A slightly more extensive involvement of the lungs than No. 3 of this series. Substernal glands slightly enlarged. Pericardium normal. Smears from lungs and substernal glands show tubercle bacilli.

INTRATHORACIC RABBITS.

Rabbit 1, March 25, Thirteenth Day.—The needle at inoculation passed through the lower point of the thoracic cavity, through the diaphragm into the abdominal cavity. There is a tubercle at the skin entrance, pleura and diaphragm all positive for tubercle bacilli. Abdominal cavity: The omentum and mesentery involved to about the same extent as intraperitoneal rabbit No. 2. The mesenteric glands enlarged and positive for tubercle bacilli. The postperitoneal glands normal. Liver shows many tubercles along anterior edge, the posterior and subsurface are comparatively free; smears positive for tubercle bacilli; spleen macroscopically normal. Smear negative for tubercle bacilli. Thoracic cavity normal. Sections of lung tissue negative. Smears from lungs negative for tubercle bacilli.

Rabbit 2, April 16, Thirty-fifth Day.—A cutaneous and pleural tubercle at point of inoculation. Smears positive for tubercle bacilli. Lungs in an advanced state of tuberculosis; cavities in both apices. Pleura and pericardium extensively involved, substernal glands only slightly enlarged, but show tubercle bacilli on staining. Smears from all mentioned organs positive for tubercle bacilli. Abdominal cavity negative.

Rabbit 3, April 8, Twenty-seventh Day.—The needle in this rabbit, at inoculation, did as in No. 1 rabbit, and there is extensive tuberculosis of the organs in both the thoracic and peritoneal cavities. As is shown in the accompanying table, this rabbit died without any conjunctival tests having been done.

Rabbit 4, May 5, Fifty-fourth Day.—A large tubercle at point of inoculation; smears positive for tubercle bacilli. Abdominal cavity negative. Thoracic cavity: Left lung shrunken and attached to pleura posteriorly, studded with tubercle. Same right lung; a large cavity in apex. Pleura and substernal glands extensively involved. Smears positive. Abdominal cavity negative.

INTRAVENOUS RABBITS.

Rabbit 1, March 26, Eleventh Day.—A small tubercle at point of inoculation in left ear. Smears positive for tubercle bacilli. Beginning tuberculosis of lungs, liver and spleen. No appreciable glandular involvement at any point.

Rabbit 2, April 10, Twenty-sixth Day.—A large tubercle at point of inoculation in left ear with a few glands at base of ear. General miliary tuberculosis involving the lungs, pleura, pericardium, substernal glands, liver, spleen, omentum, peritoneum, mesentery, postperitoneal and mesenteric glands.

Rabbit 3, April 14, Thirtieth Day.—Died. Autopsy picture practically the same as intravenous rabbit No. 2.

Rabbit 4, May 5, Fifty-first Day.—A large tubercle in left ear at point of inoculation, extending down to base and involving the glands in this region. Abdominal cavity negative. Thoracic cavity negative, except for an early tuberculosis of both lungs. We evidently did not enter the vein in this rabbit at the time of inoculation.

NORMAL RABBITS.

Rabbit 1, May 6.—Normal throughout, except for a few tubercles in left lung. Smears from lung positive for tubercle bacilli.

Rabbit 2, May 6.—Normal.

Rabbit 3, May 6.—Normal.

TOXIN RABBITS.

Rabbit 1, May 6.—Normal.

Rabbit 2, May 6.—Normal.

1822 Spruce Street, 1805 Spruce Street, 6504 Germantown Avenue.

ACIDOSIS AND ASSOCIATED CONDITIONS.*

JAMES EWING.
NEW YORK.

(*Concluded from page 354.*)

II. PHYSIOLOGIC CHEMISTRY OF ACETONE COMPOUNDS.

The significance of acidosis must eventually be determined by the chemistry and physiology of the substances in question. The enormous quantities of acetone compounds found in diabetes are of much interest, but they may be of no more importance for the symptoms of the disease and no closer index of its nature than is the enormous excretion of sugar. We believe that sugar is neither directly nor indirectly a toxic agent in diabetes, but the doctrine of acid intoxication supposes that the acetone compounds are directly responsible for some of the most striking symptoms. Indeed, if this doctrine is accepted in its entirety most of the serious symptoms of the disease must be connected with these substances. As the direct study of diabetes has not succeeded in fully establishing the position of acid intoxication, new light must be sought in the chemistry and physiology of the acetone compounds and in the general occurrence of acidosis.

The Sources of Acetone Compounds.

That a close relation exists between acetone, aceto-acetic and beta-oxybutyric acids is seen in their chemical constitution.

Beta-oxybutyric acid — Aceto-acetic acid — Acetone

It is shown also by the readiness with which acetone may be derived from beta-oxybutyric acid in the test-tube, by the appearance of diacetic acid and acetone in the urine when beta-oxybutyric acid is administered

*The Cartwright Lectures for 1908 of the Alumni Association of the College of Physicians and Surgeons, delivered at the New York Academy of Medicine, March 25, 27 and 30, 1908.

to animals, and by the frequent association of all three acetone compounds in the urine.

Minkowski in 1869, distilling a dilute solution of beta-oxybutyric acid oxydized by potassium bichromate and sulphuric acid, obtained acetone, and he concluded that in man this acid was the forerunner of acetone. Diacetic acid is readily transformed into acetone at 100 degrees C. Minkowski fed beta-oxybutyric acid to a diabetic dog; Meyer gave it to healthy men, and Waldvogel and Magnus-Levy to diabetic patients, and in each case there was an increase of acetone or diacetic acid in the urine. These results have often been verified. Characteristic of the occurrence of acetone compounds is the fact that acetone, diacetic acid and finally beta-oxybutyric acid appear in order as the disease increases in severity and disappear in the reverse order as the disease improves. There is thus abundant evidence of the close relation between these three substances, justifying the use of the expression "acetone compounds," and indicating that they all have a common source in the body. Yet there are other modes of origin of acetone besides the direct derivation from oxybutyric acid, and several discrepancies exist between this theory of origin and the occurrence of acetone bodies in the urine, so that the exclusive origin of acetone from oxybutyric through diacetic acid can not be regarded as satisfactorily proven.

Relation to Carbohydrates.

The old clinical impression that acetonuria resulted from fermentation of carbohydrates in the intestine was supported by the appearance of acetone in the test-tube when various carbohydrates were split up in the presence of alkalies (Fremy).

It has also seemed possible that the diabetic acetonuria may result from destruction of sugar or other carbohydrates of the body, since Harley found acetone and diacetic acid in the blood of dogs after injection of glucose and ligation of the ureters, and derived both those substances from sugar. Yet Pflüger regards the production of acetone from sugar in diabetes as far from proved, and it is obvious that Harley's experiments are not necessarily binding for diabetes.

That any considerable formation of acetone from carbohydrates occurs in human disease was rendered very unlikely by the discovery by Rosenfeld and Hirschfeld that carbohydrate-free diet induces marked acetonuria, and that in diabetes the withdrawal of carbohydrates may cause a large increase in acetone output which diminishes on the restoration of carbohydrates to the diet. On the other hand, in certain cases of diabetes in which the glycosuria has been reduced, the ingestion of

carbohydrates increases both sugar and acetone (Waldvogel, p. 75). In diabetes and some other pathologic conditions the acetone of the urine greatly exceeds that of the breath, while in the dietetic acetonuria of normal subjects excretion by the breath usually exceeds that of the urine and may reach 70 per cent. of the total (Schwarz). It is a curious effect of carbohydrates that they tend to increase the proportion of acetone eliminated by the breath and to decrease that of the urine, thus transforming the pathologic into a so-called physiologic condition.

Carbohydrates vary in their capacity to influence acidosis. In starvation Jorns asserts that he has observed that starch increased the acetone, but that saccharose, and, to a much less extent, glucose decreased the total acetone excretion, while glyconic acid diminished the acetone of the breath while increasing that of the urine. The striking benefit in diabetes obtained by von Noorden and others, and recently by Herrick, from the use of oatmeal and other carbohydrates, suggests that the diabetic organs may lose the capacity to burn one carbohydrate while retaining command over others. Yet the results of the oatmeal diet in diabetes have been very conflicting, and the exact cause of the improvement in such cases is not certainly known.

The marked antiketogenic influence of levulose noted by Möhr and Loeb has also been applied in the treatment of diabetes. According to Hirschfeld, at least 80 gm. of carbohydrate must be taken daily to prevent the occurrence of dietetic acetonuria, but the observations are hardly sufficient to establish any definite rule.

Two hypotheses have been suggested to account for these observations: 1, that the burning of carbohydrates facilitates the combustion of acetone compounds; and, 2, that the presence of carbohydrates spares the body fats and thereby stops the formation of acetone compounds.

Waldvogel is the chief exponent of the view that carbohydrates merely prevent the burning of fats, and in a detailed consideration of various forms of acidosis he was able to show rather clearly that acidosis usually begins with the burning of body fats. In phloridzinized dog acidosis begins after the liver has consumed its glycogen and has begun to call on the fats and proteins for energy, and here feeding protein as well as carbohydrate reduces the acidosis (Baer, Blum). It thus appears that in dogs acidosis will not arise as long as there are available carbohydrates anywhere in the body.

Yet this fact does not prove for human acidosis that the carbohydrates merely replace the fat, although it is true that carbohydrates are more readily burned in health than are fats. If the carbohydrates merely replaced fat, then there should be a quantitative relation between the

amount of sugar needed and the degree of acidosis (fat consumption) to be combatted. But, as von Noorden shows, no such relation exists, since 100 gm. of glucose, equivalent to 30 to 35 gm. of fat, promptly obliterates most traces of acidosis after meat fat diet, and the acidosis does not recur when muscular exertion raises the consumption of fat, as he supposes, above its former level. Satta shows that comparatively small amounts of carbohydrate suffice to prevent acidosis, while much larger quantities are needed to reduce it when once established. Hence it appears that the burning of carbohydrates facilitates the normal and complete combustion of fats, as though the oxidation, more readily established in carbohydrates, was communicated in some way to the fats. Möhr supposes that the carbohydrates, which are rich in oxygen, yield nascent oxygen within the cells and thus directly consume the fats, but there appears to be no definite chemical ground for this opinion. Whether the carbohydrate prevents the formation of acetone compounds or facilitates their combustion when formed is not known.

According to Satta, the formation of acetone compounds is the result of a specific disturbance of fat combustion resulting, like the excessive formation of ammonia and increase of uric acid, from injury of organ cells. In pneumonia acetone production continues in spite of added carbohydrates, increases with the fever, and subsides when the general condition improves. Möhr traces this result to the slower combustion of carbohydrates. In diabetes Möhr and others believe that there is a qualitative disturbance in fat combustion connected with the failure to utilize carbohydrates, so that from a given quantity of fatty acids more acetone compounds result than in normal metabolism.

It was thought that further light on this subject might be secured by testing the effects on acidosis of rectal and subcutaneous injection of sugar. J. Muller, Schumann-Le Clercq and Waldvogel got no influence from sugar so administered, but Satta secured results as good as with administration by mouth.

While these and other related questions still await solution, at present it appears that in addition to fat and protein sparing action, a certain amount of carbohydrate combustion is necessary for the normal processes of metabolism and that when the carbohydrate is deficient metabolism is disturbed in various ways, one of which is an abnormal and incomplete combustion of fats. An interesting suggestion in this much debated field comes from Packard, who finds that *Fundulus* embryos, maltose, levulose and glucose increase resistance to lack of oxygen, acting, according to this observer, as depolarizers in the process of protoplasmic respiration and enabling this process to go on to some extent in spite of the lack of oxygen.

Relation of Acetone Compounds to Fats.

While the final proof that acetone compounds may be derived from fats in the test-tube has been reserved for recent workers, it was shown by Cotton that fats on oxidation yield acetone, and it was partially proved by Schreiber that beta-oxybutyric acid appears when butter is warmed with potassium permanganate and alkali. The butter, however, contained traces of protein, as well as butyric acid.

Geelmuyden first observed a marked increase of acetone in healthy men fed on butter, and his observations formed the beginning of the present extensive clinical data by which the origin of acetone from fats has been proven. Having in mind the fact that acetone excretion in many cases is not accompanied by excessive destruction of proteins, and accepting the clear indication that acetone is not derived from carbohydrates, Waldvogel saw no other source for the acetone compounds than the fats, and with Hagenberg he demonstrated a definite increase in acetonuria by feeding olive oil to fasting subjects and diabetics, and by adding butter and olive oil to full mixed diet of normal subjects. Many exceptions to this ketogenic action of fat were found to be due to personal peculiarities of the subject, to the amount and character of the food in the intestine, and especially to the readiness with which the fats were absorbed.

In these earlier experiments much confusion arose from failure to take account of the antiketogenic effects of the carbohydrates. It was found that the increase of acetone in patients on mixed diet was not constant and never marked, seldom exceeding 100 mg. per diem. One of the disturbing factors was shown by Geelmuyden to be the carbohydrates of the food, while Schwarz found that administration of 150 gm. of glucose caused a prompt disappearance of acetonuria in a patient who showed acidosis from a meat-fat diet. On such a diet free from carbohydrates more pronounced grades of acidosis occur. Gerhardt and Schlesinger each subsisted on meat and fat for eight days. Acetonuria appeared on the second day, diacetic acid on the third day, and beta-oxybutyric acid in considerable amounts on the fifth and seventh days. Yet even here the presence of protein in the food diminishes the ketoplastic action of fat, since acetonuria increases as the albumin of the food is decreased (Rosenfeld). This result may be referred to the action of carbohydrate radicles in protein and to its general fat-sparing influence (Geelmuyden). Hence it appears that the ketogenic influence of fats can be satisfactorily studied only in fasting subjects.

A third disturbing factor of importance was pointed out by Joslin in the variable absorption of fats, a source of error which previous

observers had largely overlooked. It was found by Hirschfeld that, of the components of fat, glycerin is strongly antiketogenic, and Hagenburg and Joslin showed that neutral fats are not ketogenic, probably because of their glycerin content, and that the ketoplastic action of fats increases with their content of free fatty acids. The failure of palmitic and stearic acids to increase acetone, as noted by Schwarz, Joslin attributes to their failure to be absorbed, while oleic acid which is readily absorbed is markedly ketoplastic. Butyric acid he found inert in a healthy fasting subject.

In diabetics various forms of fats have been found to increase acidosis, as butter, olive oil, bacon, cream. Sodium butyrate greatly increased the acetone in a case of Schwarz. Yet Magnus-Levy gave a mild diabetic 20 gm. of beta-oxybutyric acid in three hours and the urine failed to yield any acetone compounds. Loeb and Möhr found a general parallel between the amount of fats taken by diabetics and the excretion of beta-oxybutyric acid. On giving a diabetic 50 gm. of water-free butyric acid there was an increase in the beta-oxybutyric acid excreted of 19.5 gm.

It is obvious that the above observations have a practical bearing both on the regulation of diet in acidosis and on the interpretation of the signs of acidosis. The lower fatty acids, butyric, caproic and isovaleric, are so readily converted into beta-oxybutyric and yield relatively such large amounts, as shown by Schwarz, that it seems highly desirable that these acids should be excluded from diabetic diet.

According to Schwarz, the ketogenic action of fats in severe diabetes is very little influenced by carbohydrates and increases with the loss of the capacity of the body to burn carbohydrates and fats. In a case of diabetes, in which the patient received 200 gm. of beef fat daily for three days, Schwarz saw dyspneic coma develop, and Waldvogel details a case in which fatal coma developed after a period in which the diet contained 100 gm. of butter per diem.

An interesting experiment by Satta indicates that the grade and character of acidosis do not vary whether the patient burns his own or ingested fat, since two subjects, one on a meat-fat diet, the other fasting, began to excrete beta-oxybutyric acid on the first and second days, the total excretion averaging 7.89 gm and 7.85 gm. daily over the three or four days of observation. Yet in the fasting subject the acidosis increased rather more rapidly. Allard found that the introduction of fast days in the course of diabetes caused a marked reduction of acetone lasting several days, an observation that shows that acetone compounds are rapidly produced from ingested food.

While the above clinical experiments strongly impressed the belief that fats are the chief source of acetone compounds, this opinion has long lacked a needed confirmation from the inability to trace the steps through which fats become converted into acetone compounds. This deficiency has been largely met by Knoop, who has shown that fatty acids are attacked by oxidation at the beta-carbon atom, and that, according to this rule, certain fatty acids are readily oxidized in the body to the acetone series. Knoop executed the plan of attaching the benzol ring to various fatty acids to facilitate their identification and then determining their fate in fasting dogs. In this way he was able to arrest the oxidation at certain points so as to determine the steps in the process.

If the fatty acid attached as a side chain to the benzol ring contains only two carbon atoms, as phenyl acetic acid, $C_6H_5CH_2COOH$, these can not be split off and such compounds pass through the body unaltered. If the chain contains three or four carbon atoms these can be split off, but only in groups of two. Thus:

Cinnamic acid, $C_6H_5CH{=}CHCOOH$, yielded C_6H_5COOH.

Phenyl butyric acid $C_6H_5CH_2CH_2CH_2COOH$, yielded $C_6H_5CH_2COOH$.

Phenyl valeric acid, $C_6H_5CH_2CH_2CH_2CH_2COOH$, yielded C_6H_5COOH.

On the other hand, phenylalanin, $C_6H_5CH_2CHNH\,COOH$, was completely burned, the benzol ring being split up. Phenyl lactic acid, $C_6H_5CH_2CHOH\,COOH$, and some other benzene compounds were also split up, but the conditions determining the combustion of the benzol ring have not been defined.

Knopp's beta-carbon oxidation theory has revealed for the first time a definite rule governing the oxidation of fatty acids, and if his deductions are valid then it should become possible to predict from their chemical constitution which acids will prove ketogenic. In order to yield beta-oxybutyric acid a normal fatty acid must contain at least four carbon atoms. It must contain an even number of carbon atoms in order to follow the rule of beta-carbon oxidation, with splitting off of the carbon atoms in groups of two. Thus normal valeric acid ($CH_3CH_2CH_2CH_2COOH$) does not yield beta-oxybutyric acid, while caproic acid does ($CH_3CH_2CH_2CH_2CH_2COOH$) (Schwarz).

The theory has already been tested to some extent. Embden, by perfusing excised organs with aërated blood, has found that the liver is the sole organ producing acetone under these conditions. Perfusion through lung, muscle or kidney failed to give acetone (Embden, Kalberlah).

He, therefore, located in the liver the chief function of acetone production in the body.

Embden, Salomon and Schmidt, perfusing through the excised liver aërated blood containing various fatty acids, obtained results which show that the rule of beta-carbon oxidation does not apply in the case of branched fatty acids or amino acids. Thus leucin and isovaleric acid gave increased acetone while aminovaleric acid and isobutylacetic did not.

Yet isovaleric acid, $\begin{matrix}CH_3\ CH_3\\ CH\\ CH_2\\ COOH\end{matrix}$ can not give beta-oxybutyric acid by oxidation at the beta-carbon atom. Baer and Blum obtained similar results, conflicting with this theory. Administering fatty acids to diabetics, they found that isovaleric acid, leucin, tyrosin, and phenylalanin. were ketogenic, while normal valeric acid, $\begin{matrix}CH_3\\ CH_2\\ CH_2\\ CH_2\\ COOH\end{matrix}$ and isobutyric acid, $\begin{matrix}CH_3CH_3\\ CH\\ COOH\end{matrix}$ were not.

Borchardt and Lange seem to have thrown needed light on the subject by pointing out that three rules govern the formation of beta-oxybutyric acid from fatty and amino acids:

1. Branched fatty acids yield beta-oxybutyric acid through the replacement of the methyl group (CH_3) by hydroxyl. Example:

Isovaleric acid. Oxybutryic acid.

$$\begin{matrix}CH_3\ CH_3\\ CH\\ CH_2\\ COOH\end{matrix} = \begin{matrix}CH_3\ OH\\ CH\\ CH_2\\ COOH\end{matrix}$$

Schwarz, Emden, and Baer and Blum, all found isovaleric acid ketogenic.

2. Derivatives of fatty acids and proteins, including amino-acids, may be split up by oxidation at that carbon atom at which one H is replaced by some other group. Thus:

Aminovaleric acid. Butyric acid. Oxybutyric acid.

$$\begin{matrix}CH_3\\ CH_2\\ CH_2\\ CHNH_2\\ COOH\end{matrix} = \begin{matrix}CH_3\\ CH_2\\ CH_2\\ CH_2\\ COOH\end{matrix} = \begin{matrix}CH_3\\ CHOH\\ CH_2\\ COOH\end{matrix}$$

Here oxidation occurs at the alpha-carbon atom, and since amino-acids of this type constitute the bulk of most proteins, this rule may explain the possible

ketoplastic influence of many proteins. Thus leucin passes through isovaleric acid to beta-oxybutyric acid.

Leucin.		Isovaleric acid.		Oxybutyric acid.
CH_3 CH_3		CH_3 CH_3		CH_3 OH
CH		CH		CH
CH_2	=	CH_2	=	CH_2
$CHNH_2$		COOH		COOH
COOH				

3. Normal straight-chain fatty acids follow Knoop's rule of beta-carbon oxidation, and they yield beta-oxybutyric acid only when they contain at least four and an even number of carbon atoms. Butyric and caproic acids yield beta-oxybutric acid.

Butyric acid.			Caproic acid.		
CH_3		CH_3	CH_3		
CH_2		CHOH	CH_2		CH_3
CH_2	=	CH_2	CH_2	=	CHOH
COOH		COOH	CH_2		CH_2
			CH_2		COOH
			COOH		

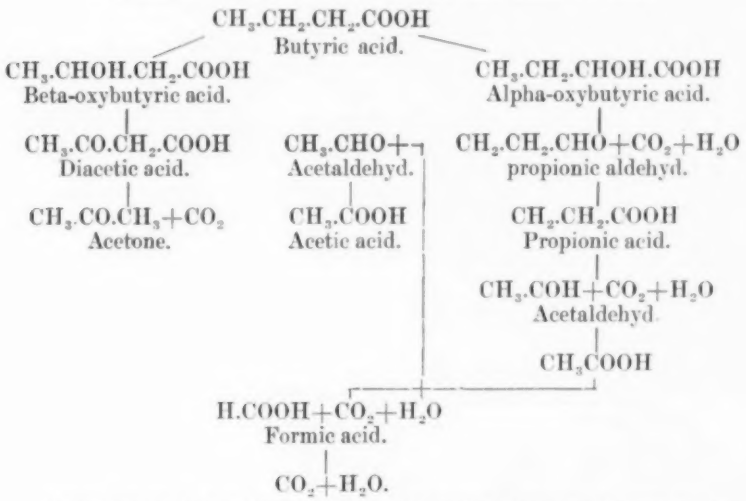
Normal valeric acid, however, is not ketogenic, oxidizing at the beta-carbon atom.

Normal valeric acid: CH_3
CH_2
CH_2
CH_2
COOH

How far these rules may explain the behavior of other fatty acids which have not been directly tested, and especially their application to more complex fat and protein derivatives, remains for future studies to determine. So far as I can learn these rules cover the observed facts.

Many of the obscurities in the working out of Knoop's theory are missing in the direct demonstration by Dakin of the steps of oxidation of butyric acid in the test-tube under the influence of peroxid of hydrogen. The convincing quality of Dakin's work consists in the direct isolation from the products of oxidation of butyric acid of a number of substances which when arranged in their necessary series reveal the steps which the process has taken. Assuming that the higher fatty acids when breaking down reach the stage of butyric acid by the rule of beta-carbon oxidation, Dakin isolated from the further oxidation of butyric acid the following substances: aceto-acetic acid, acetone, propionic aldehyd, acetaldehyd, acetic acid, formic acid and carbon dioxid. From these data the following series of changes has been reconstructed by Dakin.

DERIVATION OF ACETONE FROM BUTYRIC ACID.—DAKIN.



According to this scheme butyric acid under these conditions suffers oxidation at both alpha- and beta-carbon atoms, in the former case yielding acetone compounds, in the latter case passing through a longer series of steps, possibly including lactic acid, but eventually reaching complete oxidation with avoidance of the acetone stage. This conception of the breaking up of fatty acids applying equally to the amino-acids, opens up several lines of speculation. It would appear to be a matter of considerable consequence whether oxidation occurs at the alpha- or the beta-carbon atom, since in the former case the process becomes arrested at the acetone stage, while in the latter case, passing, as Dakin believes, through lactic acid, the process is carried to completion. Much importance may therefore attach to the decision whether oxidation shall occur at the less favorable beta-carbon atom or in the more propitious alpha position.

The significance of Dakin's work must eventually depend on the validity of reactions in the test-tube for processes occurring in the body. It is pointed out that similar products of protein decomposition result from the action of bacteria and yeasts. Yet hydrogen peroxid does not act in the body, and even in the test-tube its behavior is easily influenced. Shaffer has shown that uric acid is rapidly broken up in the test-tube by hydrogen peroxid, but on the addition of a little of the enzyme katalase, hydrogen peroxid is promptly split up and the uric acid remains unaltered.

At present we must be content to learn that such a series of changes as Dakin constructs is a possibility, while leaving to the future to decide its bearing on vital processes.

Relation to Proteins.

The possibility of obtaining acetone from proteins in the test-tube seemed to have been proved by Cotton by digesting fibrin and casein with peroxid of hydrogen, and by Blumenthal and Neuberg by heating gelatin with ferric salts and peroxid of hydrogen, while Orgler in the same manner obtained acetone from crystalline egg albumin.

The clinical observations pointing to the derivation of acetone compounds from proteins relate chiefly to diabetic acidosis. The well-known fact that diabetics respond to meat-fat diet with increased acetonuria was long accepted as proof of the protein origin of acetone, and it still remains a question whether, under these conditions, much of the acetone in diabetes is not the result of protein metabolism. The acetonuria following withdrawal of carbohydrates was also interpreted in the same direction.

On the other hand, cases of diabetes were observed, two of which were carefully reported by Weintraud and by Magnus-Levy, in which with nitrogen equilibrium, large amounts of acetone compounds were excreted over long periods. Further, Hirschfeld, Palma, and Waldvogel showed that there was usually no parallel between nitrogen and acetone excretion, and in three cases Hirschfeld found less acetone with rich than with low protein diet. When, in addition to these well-attested observations, the fat and protein sparing influence of carbohydrates became recognized, and the pronounced ketoplastic action of ingested fats had been subjected to experimental control the importance of proteins as a source of acetone appeared to be greatly reduced.

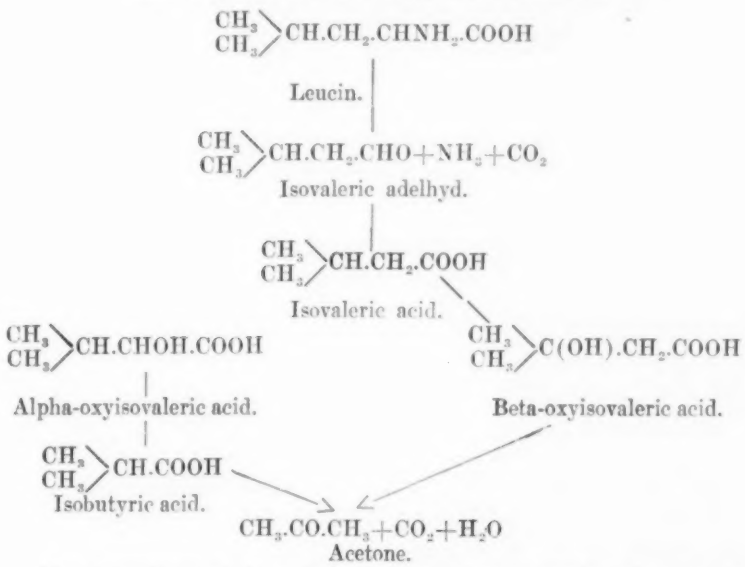
Yet several recent studies show that amino-acids are readily converted into acetone compounds both in the organism and in the test-tube.

Baer and Blum obtained increased acetonuria in diabetics fed with leucin, and Borchardt and Lange demonstrated the ketogenic influence of these substances in healthy subjects on carbohydrate-free diet. By perfusing excised livers with blood containing leucin or ammonium isovalerate, Emblem, Salomon, and Schmidt secured considerable amounts of acetone.

In the test-tube Dakin warmed leucin, alanin, and glycerol with peroxid of hydrogen and traces of ferrous sulphate and, among the products, obtained traces of acetone. From leucin the products isolated were

isovaleric aldehyd, isovaleric acid, acetone, ammonia, carbon dioxid and probably isobutyric acid, some of which have been obtained from the action of bacteria on leucin. From these substances the following series of changes from leucin could be reconstructed:

DERIVATION OF ACETONE FROM LEUCIN.—DAKIN.



Not all radicles of the protein molecule seem to produce acetone, at least in the animal body. In fact, it is clear that proteins, like fats, contain antagonistic groups as regards acetone formation. Some indication of the nature of these antagonistic radicles may be obtained from an inspection of the various protein derivatives whose relation to acetone formation has been tested.

KETOGENIC RELATIONS OF PROTEIN DERIVATIVES.

	KETOGENIC.
Leucin	Borchardt, Lange.
Arginin	Borchardt, Lange.
Aminovaleric acid	Borchardt, Lange.
Isovaleric acid	Baer, Blum.
Beta-aminobutyric acid	Sternberg.
Nutrose, casein (in diabetes)	Lüthje.
Protamin	Borchardt.
Histon	Borchardt.

Egg albumin	Borchardt.
Thyroid	Waldvogel.
Sodium butyrate	Schwarz.
Sodium acetate	Satta.
Butyric acid (in diabetes)	Loeb, Mohr.
Oxybutyric acid (in diabetes)	Loeb, Mohr.

ANTIKETOGENIC.

Alanin	Satta, Borchardt, Lange.
Lactic acid	Satta, Borchardt, Lange.
Aspargin	Satta, Borchardt, Lange.
Glutaric acid	Baer, Blum.
Glycerin	Hirschfeld.
Sugars, saccharose, glucose, maltose, mannite	Hirschfeld.
Alcohol	Neuberg.

NEGATIVE.

Glycocoll, glutaminic acid, glycolic acid, acetic acid	Borchardt, Lange, Baer, Blum.

In the above lists it is evident that the antiketogenic substances belong in general in the carbohydrate class.

Among the ketogenic substances are fatty acid derivatives, certain monamino-acids, and more complex protein compounds. The behavior of the amino-acids and the complex protein compounds presents some obscure features. While pure leucin and aminovaleric acid are ketogenic, the study of the influence of protein foods containing these acids shows that such foods are relatively antiketogenic, and in direct proportion to their content of monamino-acids. Borchardt finds that protamin, histon, egg albumin, pancreas and casein contain monamino-acids increasing in the order named, and that in healthy subjects showing acetonuria from carbohydrate-free diet protamin markedly increases acetone, while casein reduces it. Likewise Rosenthal finds that meat, casein, egg albumin, and thymus, added to rich protein diet, all increase acetone, but the increase is least with casein which contains the highest proportion of monamino-acids. It is, therefore, necessary to suppose that proteins contain antiketogenic as well as ketogenic radicles.

Certain antiketogenic radicles of proteins are not difficult to trace, since they appear in the carbohydrate reactions which have long been recognized and are divided among the hexoses and pentoses, etc. In egg albumin Müller and Seeman estimate that 20 per cent. of the carbon is in the form of radicles with carbohydrate tendencies.

The position of the monamino-acids in this respect is uncertain. The fact that in pure form leucin is ketogenic shows that these acids act as sources of acetone. Yet the relatively antiketogenic influence of pro-

teins rich in monamino-acids indicates that in their natural relations these acids tend to act more like carbohydrates and reduce acetone. Possibly in different conditions they may turn in either direction.

The following table from Rosenthal exhibits these general relations, showing that the higher the glycogen-producing quality and the content of monamino-acids, the less is the production of acetone.

KETOGENIC RELATIONS OF PROTEINS ON RICH PROTEIN DIET—(Rosenthal).

Protein substance.	Glycogen forming capacity.	Monamino-acid N Kossel-Kutscher.	Acetone excretion.
Meat	Abundant.	Rich.	899 mg.
Casein	3.09 %	53.70 %	1113 mg.
Egg albumin	1.97 %	50.40 %	1498 mg.
Thymus	0.284 %	26.88 %	1863 mg.

In diabetes the influence of these proteins will depend on the extent to which carbohydrate combustion is lost. Thus Lüthje found that calf thymus, poor in monamino-acids, reduced diabetic acidosis, while casein, rich in these acids, usually increased the acidosis. Here the monamino-acids appear to be ketoplastic. There is, therefore, evidence indicating that leucin acts differently in diabetes and in health, and that its behavior when given in pure form may vary from that observed when it is administered in the whole protein.

The work in this field reaches a practical bearing in the choice of protein foods which may inhibit acidosis. It is well known that the various proteins, especially those of vegetable origin, differ enormously in their content of monamino-acids. Quantitative analytic methods for this work are not yet fully available, but the contributions of Fischer, Müller, Hausmann, Kossel, Abderhalden, Osborne and Barker reveal from this standpoint a new outlook for rational dietetics. It is known that the common meats do not differ greatly in monamino-acids, which constitute 60 to 66 per cent. of these proteids, but in thymus the proportion is below 50 per cent.

The demonstration that proteins contain abundance of acetone-formers does not assure that they figure prominently as a source of acetone in disease. Their relation to the different forms of acidosis has to be determined by direct observation, and the present tendency is to attribute to proteins a very subordinate rôle as sources of acetone; but the recent studies in protein chemistry have reopened the whole question, which seemed at one time practically settled in favor of the fats.

RELATION OF ACETONE COMPOUNDS TO AMMONIA.

According to the theory of acid intoxication, increased excretion of acetone compounds should be accompanied by increased excretion of

ammonia. In the majority of cases of acidosis, especially in diabetes, this relation holds and the ammonia excretion has come to be regarded as the measure of acidosis. Yet the exceptions to the rule are so numerous and striking as to raise grave doubts regarding a necessary relation between ammonia and acetone compounds and acidosis in general.

Limbeck has shown that excessive doses of alkalies do not remove all ammonia from the urine, which must have other functions than the neutralization of acids. In many cases of diabetes and other diseases associated with acidosis, ammonia excretion is considerable while acetone compounds are scanty or absent. In acidosis the ammonia bears relation not only only to the organic acid excretion, but also to the total nitrogen excreted, so that in any attempt to estimate acidosis from ammonia it becomes necessary to consider not only the absolute quantity but also the percentage of nitrogen excreted as ammonia.

Satta has considered in detail the relation between ammonia and acetone compounds in healthy subjects on carbohydrate-free diet. On feeding glycerin or fats under such conditions the ammonia-acetone compound ratio varied excessively, the acetone compounds rising far out of proportion to the ammonia and the ratio falling. An influence of excessive inorganic acids in the food was eliminated, since these remained constant. The increase of ammonia occurred on the first day of the experiment, although the blood contains alkali capable of neutralizing 80 gm. of beta-oxybutyric acid. In diabetes, 20 gm. of sodium bicarbonate failed greatly to influence the ammonia or the acetone compounds, although the amount of alkali given was sufficient to neutralize more than the total quantity of acetone compounds.

AMMONIA: ACETONE COMPOUNDS RATIO. SATTA.

Urine, c.c.	S. G.	N.	NH^3.	Acetone cmpds. as oxybut. acid.	NH^3: acetone cmpds.	Diet.
2290	1.010	14.4	0.856	0.95	.90:1	Meat.
1930	1.010	10.8	1.42	1.91	.74:1	Meat.
1660	1.015	10.9	2.51	8.73	.28:1	Meat.
2150	1.011	10.7	3.40	20.0	.17:1	Meat.

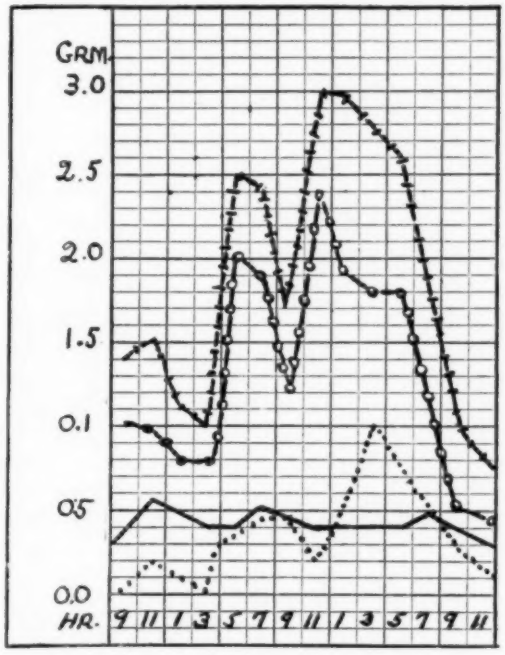
In a second case of diabetes 40 gm. of sodium bicarbonate reduced the acetone compounds to a trace, although 2.64 gm. of ammonia (= 13.2 gm. beta-oxybutyric acid) were excreted.

Allard also has emphasized the very loose relation existing between NH_3 and beta-oxybutyric acid in diabetes when the hourly variations are followed, observing that on meat-fat diet the ammonia does not follow the variations in acetone compounds, while on hunger days the ammonia

rises, although the acetone compounds diminish. The influence of the alkalies of the food may in part explain these discrepancies.

HOURLY EXCRETION OF ACETONE COMPOUNDS AND AMMONIA IN SEVERE DIABETES, ON MEAT-FAT DIET. ALLARD.

Hence Satta concludes that the ammonia formation in acidosis is largely the result of a specific disorder of nitrogenous metabolism and is not merely concerned with neutralization of acids. While regarding



—|—|—|—|— Total acetone compounds.
o—o—o—o—o Beta-oxybutyric acid.
——————— Ammonia nitrogen.
..... Acetone.

the ammonia as an index of the disturbed nitrogenous metabolism, he would consider the acetone compounds as a measure chiefly or exclusively of disturbed fat metabolism. An uncertain element in these deductions is the possible presence of acids not considered in the computations. The ammonia excretion in other forms of acidosis bears on this question

and will be considered later. Here it may only be suggested that the estimation of acidosis by ammonia excretion is an indirect and often very unreliable measure of acidosis and is an especially uncertain index of any particular type of acidosis.

Intestinal Origin of Acetonuria.

The whole subject of the exact sources of acetone would lose much interest if it should transpire that any considerable degree of acetonuria is of intestinal origin. This was, indeed, one of the earliest interpretations of acetonuria, being introduced by Lorenz in 1891, and being once widely accepted as the probable explanation of many toxic symptoms accompanying gastrointestinal disorders. Against the intestinal origin of the acetone compounds in gastrointestinal diseases stood the prominent fact that the patients were usually imperfectly nourished, and Waldvogel has clearly emphasized the importance of starvation and burning of body fats in these cases. Moreover, the direct examination of the stools failed as a rule to show a sufficient depot for the urinary acetone. Yet Müller reports the presence in Cetti's stools of 1.21, 0.57, 1.14 gm. of fat, one-half neutral fats and cholesterin, the other half free fatty acids and soaps. In Nebelthau's case, with 24 to 43 mg. acetone in the daily urine, the feces (108 gm. dry) contained 0.103 gm. of acetone. In addition to the element of starvation, Satta considers the influence of absorbed toxic substances to be of considerable importance in this form of acetonuria.

The prompt antiketogenic action of carbohydrates has been considered as favoring the intestinal origin of acetone, but this rapid influence is undoubtedly connected with the easy absorption of many carbohydrates. Likewise, the failure of sugars, when introduced by rectum, to influence acidosis has been set aside by Satta, who finds that sugars administered by rectum are antiketogenic if given in considerable doses and properly absorbed. Definitely against the theory of intestinal origin of acetone is the fact that cathartics and intestinal antiseptics, such as benzol and salol, frequently fail to influence acidosis or may even increase it. In diabetic coma Magnus-Levy and Geelmuyden found less acetone proportionally in the intestine than in the organs. In diabetes, as in cyclic vomiting of children, the acetone in the stools and occasionally in the vomitus is most probably an evidence of excretion by these channels.

If acetone is derived from decomposition of protein food, then it should run parallel with sulphur excretion. Yet no such parallel but rather the opposite relations appears in the observations of Cetti.

In starvation acetone increases steadily during the first week while the intestinal contents diminish: the intestinal canal does not contain enough protein in starvation to yield 10 gm. beta-oxybutyric acid, the amount excreted by Cetti, while an origin from intestinal fat is excluded by the scanty content of the stools in fats.

Finally, the enormous amounts of acetone compounds in diabetes on fasting days seem to exclude an intestinal origin and point to processes of internal metabolism as the sole source of the compounds. Hence, with the increasing knowledge of the factors influencing acidosis, the theory of intestinal absorption has steadily lost ground, and is to-day quite generally abandoned.

Toxicity of Acetone Compounds.

The foregoing review of the sources and relations of the acetone compounds warrants the conclusion (now generally accepted) that these substances result chiefly from the incomplete and probably abnormal burning of fats induced by the absence of carbohydrates. The sugar-hungry cell—to use the apt expression of Lusk—turns to the fats for energy and secures it at the expense of a disordered and incomplete oxidation. In diabetes probably a considerable proportion of the acetone compounds come from the deamidized fatty radicles of the protein molecule, but in other conditions important protein sources of acetone have not been demonstrated.

Having traced the origin of the acetone compounds, the important question of their physiologic action remains to be considered. Are there reasons for supposing that the acetone compounds are directly toxic and can the symptoms associated with acetonuria be referred to the direct toxicity of these substances?

It was von Jaksch's opinion in 1885 that acetonemia was the direct cause of a great variety of symptoms associated with acetonuria, but numerous studies of the toxicity of acetone before that time, especially those of Kussmaul, and many subsequent reports have succeeded in showing that acetone acts much like alcohol or chloroform, occupying an intermediate position between these two narcotics; that it is incapable of inducing the nervous symptoms of fever, gastroenteritis, carcinoma, psychoses, or of other conditions marked by acetonuria; that it is quite incapable of producing the symptoms of diabetic coma, and that the doses required to produce symptoms in man or experimental animals exceed the amounts excreted even in diabetics. Twenty grams, or 0.08 gm. per kilo (Röhrig), produce only transient somnolence in man, while 0.2 gm. per kilo causes only mild intoxication. In dogs Schwarz caused seven

intoxication with 15.3 gm. by mouth. Dreschfeld observed no symptoms after taking 20 gm. of acetone, or after giving moderate doses to diabetics, but five or six injections of 10 minims of acetone in rabbits produced coma, slow breathing, convulsions and albuminuria. He concluded that acetone is non-toxic to healthy animals, but in disease when excretion was diminished he thought it might be responsible for serious symptoms, even those of diabetic coma. Yet the symptoms he produced were not those of diabetic coma, while the doses employed were far larger than occur in diabetes.

I have given acetone to healthy rabbits subcutaneously, 6 gm. daily, for three to five days, causing dulness and drowsiness, with slight albuminuria and acetonuria. After twelve days death occurred in one instance with emaciation and drowsiness but without coma and without fatty changes in the liver or kidneys. The urine was always alkaline, with slight acetone, and a very heavy precipitate of carbonates.

With the idea that acetone might prove more toxic in animals with fatty liver, I anesthetized a white rabbit very deeply with chloroform for thirty-five minutes, and on the following day three times for periods amounting to forty-five minutes in all. The animal recovered with great difficulty. On the following day 2 gm. of acetone at one injection failed to produce any symptoms except marked acetonuria, and 4 mg. daily on successive days were also without effect.

Negative results from the injection of acetone compounds in healthy subjects or even in diseased animals may be inadequate to decide its action when spontaneously arising in the course of the disease, but the futility of attempting to refer diabetic coma to this agent has been generally admitted. Its possible relation to milder symptoms in various diseases must be determined by future studies. At present its behavior in disease, the lack of relation to the severity of the process, its absence in many cases which show characteristic symptoms, and abundance in other cases free from signs of intoxication, do not favor the belief that it is a prominent factor in any symptom-complex in man.

With aceto-acetic acid very conflicting results have been reported. Von Frerichs, von Jaksch, Albertoni, and Dreschfeld found it non-toxic in man, even in excessive doses.

The optically inactive beta-oxybutyric acid has been tested by a large number of observers, especially by Sternberg in large doses, 10 to 12 gm., in healthy men and animals, and in diabetics, with nearly uniform failure to produce symptoms of intoxication, although the acid is a decided local caustic. With the optically active acid from diabetic urine Minkowski and Schwarz failed to detect toxic symptoms in normal or

diabetic dogs. Waldvogel was able to introduce 2.2 gm. of the acid intravenously in the phloridzin-poisoned rabbits without symptoms, although much smaller doses twice proved fatal. Subcutaneously 1.1 gm. caused hemorrhagic nephritis and death in two days. Herter, by slowly infusing into the femoral vein of monkeys large amounts of a 4 to 5 per cent. solution of beta-oxybutyric acid in normal salt, produced narcosis, but he was uncertain as to the exact significance of this experiment.

More recently Wilbur infused rabbits at the rate of 4 c.c. per minute with N/10 sulphuric acid, acetic acid 2 per cent., lactic acid 5 per cent., and beta-oxybutyric acid 5 per cent., producing with all characteristic symptoms of fatal acid poisoning. The fatal dose with each acid was uniform, the sulphuric acid being five times as active as beta-oxybutyric acid, of which 0.03152 c.c. of 5 per cent. solution per gram of body weight was fatal. Of sodium beta-oxybutyrate 0.116 c.c. of 5 per cent. solution per gram of body weight was fatal. After giving 75 c.c. of sodium salt, 24 c.c. of 5 per cent. free beta-oxybutyric acid was given, causing convulsions and death. Even 5 c.c. of the acid after the usual dose of sodium salt was very toxic. Wilbur, therefore, concludes that the salts of beta-oxybutyric acid are toxic, and that in diabetes the action of this acid is not all due to its acid properties.

Reference may again be made to the experiments of Harley, who produced in dogs coma like that of diabetes by ligating the ureters and injecting 8 to 12 gm. of glucose per kilo. The glucose disappeared from the blood in four to six hours and at the same time coma developed and deepened as the glucose diminished, while the blood alkalescence and carbon dioxid decreased and lactic acid increased from 0.09 per cent. to 0.134 per cent. The symptoms were referred to acid products of glucose.

Sternberg produced in dogs a condition resembling diabetic coma by infusions of aminobutyric acid, but this substance is probably not a natural product of intermediary metabolism.

Familiar objections meet all these attempts to duplicate diabetic coma experimentally. It is generally recognized that the rapid introduction of large quantities of acids into the blood is too crude and the factors involved are too complex to render the experiment convincing. Observations on the occurrence of beta-oxybutyric acid in disease have far more decisive value, and when 40 gm. of this acid may be excreted in one day in a case of syringomyelia on a meat diet, without symptoms of intoxication, it is difficult to maintain that this acid exerts any immediate toxic action (Gerhardt, Schlesinger).

As an indirect effect of the long-continued excretion of acetone compounds must be considered the nephritis which most observers describe

among the results of poisoning by acetone and oxybutyric acid. Ebstein and Kulz called attention to the appearance of very numerous small hyaline and granular casts in diabetic coma, and Waldvogel and others regard the appearance of such casts as a sign of excessive excretion of acids, since they have been found to disappear on feeding carbohydrates. In the experiments with hydrochloric acid, oxybutyric acid and acetone, albuminuria, casts and nephritis are nearly always noted. In clinical experience also long-continued acidosis is often followed by nephritis, especially in the toxemia of pregnancy, while nephritis is nearly constant in the terminal stages of prolonged diabetes. Many considerations of this character suggest that the acetone compounds, in addition to their acid action, are indirectly toxic through injury to the renal cells and the production of a progressive nephritis.

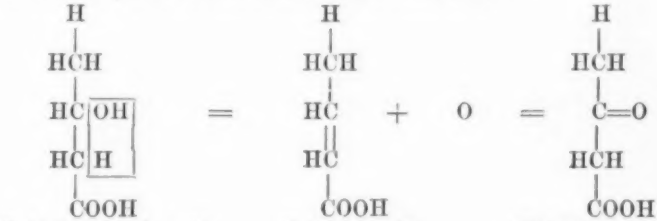
Relation of Acetone Compounds to Oxidation.

A great mass of evidence, clinical, pathologic and chemical, as well as prevailing opinion, points to deficient oxidation as concerned in the formation of acetone compounds. Clinically the diseases accompanied by acidosis are marked by excessive consumption or by deficient supply of oxygen, often by striking disturbance of respiration and by deficient general vitality, but it must be admitted that such points of view offer very uncertain data. The main basis of the theory of suboxidation is found in the general pathologic relations of fatty degeneration, which have been fully stated by Klebs and many others, and the evidence from these sources is rather comprehensive and consistent, but the further one pursues this theory in the analysis of familiar pathologic processes the less adequate it appears. It is true that in a moribund patient oxidation is less active than in health, but the statement of this fact does not add much to the conception of lethal diseases. That oxidation in many conditions does not proceed with normal vigor is undeniable, but that any definite pathologic process consists essentially in a low grade of oxidation appears still to require demonstration. As Speck concludes from a review of the chemical reactions concerned in metabolism, life does not involve simply oxidative processes.

According to Nasse, the metabolism of carbohydrates activates oxygen in the body and thereby furthers the oxidation of fatty acids to their normal end products. Yet it is difficult to see how the katabolism of glucose can liberate any free oxygen. The study of intoxication acidoses by Winterstein and Boeri led them to conclude that the assimilation of oxygen was interfered with by the poisons. Yet Lusk has shown that in phosphorus poisoning the interchange of oxygen by respiration is equal

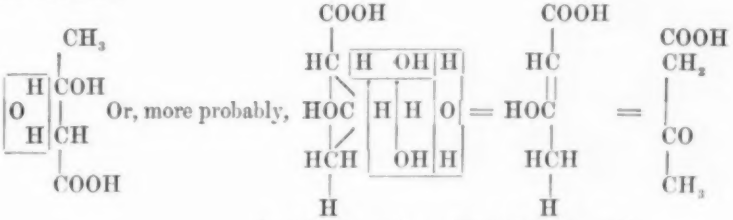
to that in health. After extirpation of the liver urea fails to be formed, but whether the defect is one of oxidation, hydrolysis, or dehydration, is not known, while the absence of specific ferments normally supplied by the liver explains the condition much more adequately than does the absence of any one chemical reaction. In diabetes there is a failure of certain processes in which oxidation is concerned, as the burning of fatty acids. Yet we do not speak of diabetes as a form of suboxidation but emphasize rather the absence of specific ferments which call into play other chemical processes as well as oxidation. Hence the ready resort to the phrase "suboxidation" in the theory of diseases of metabolism is inaccurate and misleading.

The extent to which oxidation figures in the physiologic chemistry of acidosis may be determined by the character of the reactions involved in the formation and katabolism of the acetone compounds. Here it is evident that oxidation, dehydration and hydrolysis are variously combined. In the formation of diacetic from oxybutyric acid one may assume that either the enol or the ketol form of diacetic acid is produced. In either case both dehydration and oxidation are combined.



Beta-oxybutyric acid Crotonic acid Keto-diacetic acid

With keto-diacetic acid dehydration of beta-oxybutyric and oxidation through crotonic acid are necessary. In the case of enol-diacetic acid dehydration and oxidation with formation of three molecules of water are involved.



Oxybutyric acid Enol-diacetic acid

Diacetic acid is transformed into acetone by direct hydrolysis.

$$\begin{array}{l} CH_3 \\ CO \\ CH_2 \\ COOH \end{array} + H_2O = \begin{array}{l} CH_3 \\ CO \\ CH_2 \quad H \\ \boxed{COO}\boxed{HHO} \end{array} = \begin{array}{l} CH_3 \\ CO \quad CO_2 \\ \quad + \\ CH_3 \quad H_2O \end{array}$$

It is possible, however, that diacetic acid is directly broken up by hydrolysis into two molecules of acetic acid and subsequently hydrolyzed.

$$\begin{array}{l} CH_3 \\ | \\ CO \quad OH \\ \hline\hline HCH \quad H \\ | \\ COOH \end{array} \quad \Longrightarrow \quad \begin{array}{l} CH_3COOH \\ \\ CH_3COOH \end{array}$$

Diacetic acid

Hence oxidation and hydrolysis are both involved even in the simpler final steps of formation of acetone compounds. The possibility of the synthetic origin of beta-oxybutyric acid has been discussed by several writers without definite conclusions. When one turns to the field of the earlier cleavage processes in the formation of lower fatty acids from fats and proteins the relation of oxidation and hydrolysis becomes even less certain. From the general chemical standpoint Folin expresses the opinion that the relative importance of oxidation and hydrolysis in the production of beta-oxybutyric acid is still undetermined.

Dakin's experiments in the treatment of fatty acids with peroxid of hydrogen compel the conclusion that one essential factor in his conversion of these acids into acetone compounds, etc., is oxidation, but hydrolysis is also concerned.

Confirmatory evidence that certain definite oxidative processes in the body are deficient in some diseases accompanied by acidosis is furnished by the studies of Richards and Howland on cyclic vomiting of children, and of Richards and Wallace on the influence of cyanid on metabolism, which show that in this form of acidosis neutral sulphur is notably increased. In the case of the sulphur, at least, there can be no doubt that a process of oxidation is involved.

It is impossible here to enter further into the complex ramifications of the subject of the general significance of oxidative processes in the body. It must suffice to point out that in acidosis, while deficient oxidation is an essential element, it is only one of several factors involved.

Physiology of Lactic Acid.

Although lactic acid $\begin{array}{l} CH_3 \\ CHOH \\ COOH \end{array}$ is chemically a fatty acid, it is much

more closely connected with the carbohydrates and proteins than with the fats, from which, however, Dakin obtained it by warming higher fatty acids with hydrogen peroxid. It is produced chiefly in the muscles, probably from carbohydrates (glycogen, glucose), and is either burned in the muscles or carried to the liver for combustion. In phloridzinized dogs 70 per cent. of ingested lactic acid may be synthesized to glucose. Lactic acid may also be derived from glucose by the action of a ferment contained in animal tissue (Stocklasa). Embden obtained much lactic acid by perfusing blood through a liver containing glycogen, but less when the liver was free from glycogen. Hence, Mandel and Lusk point out that a series of transformations exists—lactic acid, glucose, glycogen, glucose, lactic acid.

In herbivora lactic acid readily appears in the blood and urine in large amounts. After extirpation of the liver in geese, Minkowski found 3.5 gm. in the urine of the eighteen hours during which the animal survived the operation; it was combined with ammonia, with which it replaced the bulk of uric acid. Here it resulted from the loss of synthetic function of the liver. In this case the lactic acid must have been derived from proteins since it was proportional to the nitrogen excretion and was not increased by giving carbohydrates. Protein derivatives, like alanin and leucin, are readily convertible into lactic acid by hydrolysis.

In rabbits with strychnin tetanus it is abundant in the urine, greatly reduces the carbon dioxid content and titratable alkali of the blood, and leads to an extreme acidosis (Araki). Here it is a product of excessive muscular activity, while the deficient oxidation which results from the great dyspnea of strychnin poisoning permits it to escape oxidation and appear in the urine. Similar results appear in man after epileptic convulsions and in soldiers after exhausting marches (Inouye, Saiki). Yet carnivora burn lactic acid much more actively than herbivora and also enjoy the sources of ammonia as a protective mechanism, and it is doubtful if any dangerous grades of acidosis from lactic acid occur in man.

Kraus has pointed out that those conditions in which beta-oxybutyric acid is prominent fail to show much lactic acid. This fact is partly owing to the difference in the sources of lactic acid and of the acetone compounds. Lactic acid also has a pronounced antiketogenic influence. There is, therefore, a definite chemical, physiologic, and clinical antagonism between these two forms of acidosis, and this principle I believe may furnish a basis for the classification of diseases associated with acidosis.

The mechanism concerned in the production of lactic acid and its appearance in the blood and urine is probably a special form of defective oxidation. According to Hoppe-Seyler all tissues containing glycogen or

glucose produce lactic acid when imperfectly supplied with oxygen. Araki in a series of experiments has endeavored to establish this principle in the production of lactic acid. By slow partial asphyxia, poisoning by carbon monoxid, curare, strychnin, morphin, amyl nitrite, phosphorus, and arsenic, he has found moderate or large amounts of lactic acid in the blood and urine, often with glycosuria, and has traced the influence of deficient supply of oxygen in these conditions.

Whether quantitative deficiency or the inability of the cells to appropriate the oxygen is the essential factor is uncertain.

In hydrocyanic acid poisoning oxygen is in excess, but the cells can not appropriate it (Geppert). After extirpation of the liver it would appear that special ferments or other factors must be deficient.

In phosphorus poisoning the classical type of defective oxidation is believed to exist. Lusk has shown that in phosphorus poisoning in dogs the interchange of oxygen by respiration is normal, but it is still possible to suppose that while the respiratory currents are normal part of the oxygen is diverted from normal oxidative functions to an excess of intermediary processes of metabolism so that some oxidative processes are not carried to completion.

Although in dogs with Eck fistulas the ammonia seems to be an immediate result of the loss of urea-forming function of the liver, in phosphorus poisoning the ammonia appears to be somewhat dependent on the presence of lactic acid. Ray, McDermott and Lusk, by administering phloridzin to phosphorus-poisoned dogs, caused both the ammonia excess and the lactic acid to disappear simultaneously. Now the effect of the phloridzin is merely to prevent the formation of lactic acid, in the absence of which acid there would be no need of ammonia. Hence, the disappearance of ammonia after phloridzin poisoning would seem to indicate that the ammonia was not the direct result of injury to the liver, but was only a protective agent against the lactic acid. Yet it appears possible that phloridzin may also inhibit desamidation and thus diminish the ammonia. In either case the lactic acid and ammonia signify defective action of the liver, in the first instance from the lack of urea formation, in the second from failure to burn lactic acid, both of which functions the normal liver accomplishes.

Lactic acid appears to exert a controlling influence over fatty infiltration of the tissues. Rosenfeld finds that there is a physiologic antagonism between glycogen and fat deposit in the liver. When this organ has abundance of glycogen at command visible fat is not present, but when glycogen is lacking it must have fat for the supply of heat, and drawing it from the fat depots, visible fat appears in the liver cells.

In fasting phloridzinized dogs acidosis begins only after the liver has consumed its glycogen and has begun to burn fats and proteins.

When lactic acid appears in the urine it is a sign that glycogen is not completely burned. Under such conditions fatty changes in the liver are very constant. According to Lusk the "sugar-hungry" cell attracts fat in larger quantity than can be burned, so that a deposit of fat occurs in the cell. Hoppe-Seyler and Araki find that diminished oxygen supply results in the appearance of lactic acid. For this reason, therefore, lack of oxidation must result in fatty degeneration.

In diseases terminating in prolonged dyspnea fatty degeneration of the centers of liver lobules may or may not occur. It would be interesting to trace the relation of lactic acid in such cases. In fact, association of lactic acid in the urine with extensive fatty degeneration of the organs in many diseases deserves more thorough study. In diabetic dogs fatty liver and lactic acid in the urine are usually observed (Lusk), but in human diabetes fatty liver is rare, and Magnus-Levy believes that in this disease lactic acid occurs in negligible quantity. The reason for this difference, if it exists, may perhaps be found in the fact that dogs are less accustomed to burn carbohydrates in the food and may more readily lose all capacity to do so. Throughout the clinical forms of acidosis lactic acid and fatty degeneration are always associated.

Summary.

Having sketched in some detail the form and sources of our knowledge of the substances concerned in acidosis, it remains to emphasize in summary the main results in this field.

1. While all classes of foodstuffs yield acetone compounds in the test-tube, yet in the body these compounds are derived mainly from the fat tissues and to a less extent from the food. In diabetes, however, the proteins contribute directly or indirectly to the formation of acetone compounds. To what extent the proteins are drawn on in other conditions remains uncertain.

2. The complete combustion of fats requires the simultaneous katabolism of carbohydrates, in the absence of which there is a defective and possibly abnormal course of fat combustion lodging in the acetone compounds. In all known conditions, even in diabetes, the metabolism of carbohydrates occupies a controlling position in this form of acidosis.

3. Oxidation of straight-chain fatty acids occurs at the beta-carbon atom, so that such acids with an even number and at least four carbon atoms may yield beta-oxybutyric acid. Oxidation of pure fatty acids in the test-tube may occur at the alpha-carbon atom, with avoidance of

acetone compounds, but whether this course may be followed in metabolism is uncertain. From branched fatty acids a methyl group may be replaced by hydroxyl, and in amino-acids oxidation occurs at any carbon atom holding an amino group, both of which processes may yield beta-oxybutyric acid.

Knoop's work and the ready destruction of oxybutyric acid in healthy men indicate that this acid is a normal product of metabolism.

4. The urinary ammonia is influenced by the total nitrogen excretion, by the presence of fatty acid derivatives, by lactic acid, possibly by inorganic acids, and notably by defective synthetic functions of the liver. It bears rather loose relation to the acetone compounds, and, being an indirect measure of the presence of acids, can not replace their direct estimation.

5. The grounds are still inadequate to support the view that acetone compounds, as they arise in the body, exert any notable direct toxic action.

6. Oxidation and hydrolysis are both concerned in the formation of acetone compounds.

7. Lactic acid is a product of disordered or defective katabolism chiefly of glycogen; it results also from disturbed function of the liver, and bears an important relation to fatty degeneration.

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III. CLINICAL TYPES OF ACIDOSIS.

The Acidosis of Starvation.

One of the most significant forms of acidosis, and one that gives the clue to its origin in many diseases, occurs when the supply of food, especially of carbohydrates, is deficient. The purest examples have been shown by the professional fasters, Cetti, Breithaupt and Succi. In them acetone rapidly increased from the normal trace to a pronounced reaction a few hours after the fast began, reaching 0.5 gm. on the first day in Cetti, but only 0.054 gm. with Breithaupt, in whom the rise to 0.5 gm. required five days. The highest excretion was 0.784 gm. In many other healthy fasting men these limits were not exceeded, and often the acetone has been much lower (Müller, Senator, Hirschfeld, Waldvogel). In health most acetone (80 to 98 per cent.) (Geelmuyden) passes out by the breath, but in starvation the non-volatile forerunners of acetone can not be readily exhaled from the lung, but are usually excreted unchanged in the urine, which thus becomes the chief channel of exit.

There are, however, striking exceptions to this rule, as in Nebelthau's case, in which only 10 per cent. of the acetone appeared in the urine. In any event, to the urinary acetone must be added 20 to 40 per cent. or more to give the total excretion in starvation.

Yet the results of the sudden withdrawal of all food in the average human being are often more pronounced. Mayer found 1.90 gm. of acetone in the urine of a fasting girl with a gastric ulcer. Diacetic acid

usually appears on the first day of starvation and becomes pronounced in thirty-six hours (von Noorden). Great variations in the excretion of beta-oxybutyric acid in starvation have repeatedly been noted and may be attributed to the varying supply of carbohydrate in the body, the amount of fat in the food, the extent of the depot fat, and to individual peculiarities. In a case of hysterical vomiting Gerhardt and Schlesinger found 40 gm. in one day's urine, L. Mayer 16.3 gm. in a case of gastric ulcer, and Brugsch records 9.27 to 13 gm. from the twenty-third to the thirtieth days of starvation in a professional fasting woman. These amounts are fully equal to those observed in many cases of acid diabetic coma.

It is not justifiable, however, to regard such cases as examples of simple starvation. Patients with gastric ulcer, esophageal stenosis, and hysteria, are not normal subjects for studies in metabolism, and many secondary factors exist to intensify the influence of fasting.

During the acidosis of acute starvation there is increased excretion of calcium and phosphoric acid, the fat in the blood is sometimes increased (Cohnstein, Michaelis), but the alkalescence and carbon dioxid content have been found practically normal.

The urinary ammonia usually runs parallel with the acidosis. In a muscular man with gastric ulcer von Noorden found 8.6 gm. of total nitrogen, of which 18 per cent. was excreted as ammonia. Brugsch found 35.3 per cent. of ammonia nitrogen (1.46 gm.) in one day of Succi's fast, and an average of 21.3 per cent. (1.4 gm.) from the twenty-third to the thirtieth day. Higher ratios usually belong to cases like Nebelthau's (66 per cent.), in which the total nitrogen is very low. According to Bonninger and Mohr, the ammonia excretion in fasting is far from sufficient to neutralize the oxybutyric acid in the urine, so that fixed alkalies are from the first required for this purpose. Yet Brugsch obtained entirely opposite results with Succi.

A remarkable case of chronic starvation without acidosis is reported by Brugsch of a woman of 56 years, weighing 32 kg., extremely emaciated from esophageal stenosis, who had taken no food by mouth for nineteen days before death after gastrostomy, and who showed complete absorbtion of depot-fat. The urine gas gave no trace of acidosis and the ammonia nitrogen before the operation was 0.15 gm. or 2.9 per cent. of the total nitrogen (5.46 gm.). This observation does not support the idea of a toxic origin of ammonia in starvation, but it does show that starvation without fat consumption may be free from acidosis.

Starvation acidosis is not limited to patients abstaining from all food, but very marked grades commonly result from exclusive meat-fat diet. Yet in complete starvation the acetone compounds tend to increase, while

on meat diet the body may learn to burn fats without carbohydrates or to appropriate the carbohydrate groups of proteins; and then the acidosis diminishes.

According to Marum, in fasting phloridzin-poisoned dogs, acetonuria appears only after the liver has become free from glycogen, and disappears coincidently with the reappearance of glycogen in the liver. Very large amounts of protein in carbohydrate-free diet tend to reduce acidosis. Dogs are more accustomed than man to lack of carbohydrate and are able to burn fats without their aid. Hence, in these animals partial starvation causes little or no acidosis so long as nitrogen equilibrium is maintained. Even in depancreatinized or phloridzin-poisoned dogs there is no acidosis until negative nitrogen balance indicates the destruction of body proteins for the supply of energy (Baer, Brugsch and Bamberg).

Gerhardt and Schlesinger subjected themselves to a rigid meat and fat diet for eight days. Acetone was abundant on the first day, diacetic acid appeared on the second, and, on the fifth and seventh days, oxybutyric acid, of which 9 gm. were excreted. They reported no symptoms of intoxication.

It is characteristic of the acidosis of starvation that it is quickly relieved by carbohydrate, the administration of 100 to 120 gm. of sugar reducing the acetone in a few hours and bringing it to the normal usually within two days. Waldvogel kept a strong man four days on 1½ liters of beer and 750 gm. of white bread without increase of acetone, and Rosenfeld saw no acetonuria in a subject taking nothing but 145 gm. of cane sugar in one day. Hence, it is not the lack of food, but the absence of carbohydrates which determines the occurrence of acidosis in starvation. Yet the high acidosis with meat diets and the comparatively low grades observed in emaciated starving patients bear out Waldvogel's assertion that the degree of acidosis depends on the extent of consumption of fats.

An important question in starvation is its effect on the general vitality of the organs. Is the acetonuria purely the result of disturbed chemical reactions in the body, or are the organ cells injured by this condition and their functional capacity reduced? Numerous interesting data bear directly on this question.

Schondorff perfused the livers of recently fed dogs with blood containing the products of digestion and found considerable formation of urea; but when the liver of a starving animal was perfused with the same blood urea was found in greatly reduced amount or not at all. Schondorff concludes that the liver in starvation shows greatly reduced capacity to form urea from the normal products of digestion. Folin, however, thinks

that the amount of urea formed during perfusion through the legs of the well-fed dog was too small to justify Schondorff's conclusion. Geelmuyden found that in men on carbohydrate-free diet or fasting, 5 to 6 per cent. of diacetic acid ingested fails to be broken up, but in the same subjects on mixed diet only 0.75 per cent. escapes destruction.

While a very small quantity of carbohydrate (80 gm. glucose, Hirschfeld) is sufficient to prevent acidosis, according to Satta much larger amounts are needed to relieve an already established acetonuria. While the urinary ammonia increases with the acidosis in starvation, the observations of von Noorden (p. 51) and Satta fail to show a uniform relation between the ammonia nitrogen and the grade of acidosis in fasting. Satta shows clearly that the administration of carbohydrates in fasting promptly relieves acetonuria while the ammonia remains high for twenty-four to forty-eight hours longer. These results indicate that the withdrawal of carbohydrates causes a disturbance of cellular vitality with alteration in intermediary nitrogenous metabolism, increased excretion of ammonia, and imperfect combustion of fatty acids.

In observations on a professional faster, Cathcart found the residual nitrogen low (0.15-065 gm., 1.09-6.83 per cent.) and with a tendency to decline. Brugsch also obtained a low proportion of residual nitrogen in a professional faster. Yet in many diseases in which inanition is prominent, especially in the toxemia of pregnancy, the residual nitrogen is very much higher (Ewing and Wolf), indicating either that these are not cases of pure starvation or that starvation here takes on a toxic character. E. and O. Freund found only 56 per cent. of urea nitrogen on the twenty-first day of a fast, and they assume that the residual nitrogen made up the bulk of the remainder. Yet for the total nitrogen excretion of this case, 2.84 gm., this proportion of urea is normal, and much of the remaining nitrogen must probably be credited to creatin and creatinin, which were not estimated.

With deficient functional capacity of the liver the considerable excretion of indol and phenol from intestinal putrefaction becomes of considerable importance as indicating a possible source of secondary toxic agents in starvation (cf. Baumstark and Mohr).

Albuminuria is of very common occurrence in starvation and points to an injury of the renal cells. Von Noorden observed a case with traces of albumin on the third day of fasting. On the fourth day broth and four raw eggs were taken. Marked albuminuria followed, lasting twelve hours. Next day, on full mixed diet, albumin was absent and later when broth and seven raw eggs were taken, it failed to appear. Von Noorden

regards this observation as proving that starvation injures the renal epithelium.

The pathologic anatomy of starvation forms a very scant chapter in the extensive literature of this subject. Intestinal hemorrhages have often been observed in man and animals, and, as in Schulz's experience, fasting dogs sometimes suddenly collapse and die with intestinal hemorrhages, signs of severe intoxication, and increased nitrogen output. Delafield has long recognized in New York cases of vagabondism and starvation in which, with remarkable lack of ordinary fecal matter in the intestine, there is pronounced hemorrhagic gastro-enteritis. I have always regarded these cases as illustrating a form of autointoxication terminating starvation.

It is a widely prevalent impression that the withdrawal of food may be permitted with safety, prolonged with considerable impunity, and its consequences disregarded or estimated as a mere passing inconvenience which may be terminated at will. The study of metabolism, however, sharply contradicts this opinion, showing that starvation does not merely entail a quantitative reduction of energy, but may profoundly disturb the entire course of metabolism, lead to secondary changes in the structure of organs, and initiate a progressive autointoxication from which recovery is often slow and sometimes impossible. The observations on professional fasters can not serve as a standard for the effects of starvation in disease. Clinical experience has long established the danger of withdrawal of food in infants and children, has always recognized obese subjects as bad risks in acute infectious diseases, appendicitis and other surgical affections requiring anesthesia and operation, and has placed overnutrition in the front rank of predisposing causes of fatal autointoxication. In all these conditions it is evident that the sudden burning of body fats may constitute a serious danger to life, from loss of control of the manifold chemical reactions concerned in the process.

Acidosis in Pregnancy.

Acidosis in disorders of pregnancy first came into prominence as a diagnostic sign of fetal death. Vicarelli in 1893 examined the urine in 137 cases of gestation and found acetonuria in nine; all these patients were delivered of macerated fetuses. He naturally concluded that acetonuria was a diagnostic sign of fetal death and finding the acetone in the liquor amnii he supposed that it must come from the fetal tissues. He did not examine the urinary distillate and when this was done by Knapp, Couvelaire, and Mercier and Menu, it appeared that acetonuria occurred in many normal cases, especially at term, was more frequent

with various complications before and after labor, and was especially pronounced in eclampsia, and with some but not all cases of fetal death. Couvelaire considered acetonuria a sign of autointoxication.

Scholten, in a study of 33 cases, observed acetonuria in 31 at the puerperium, increasing with the length and severity of labor. Markedly increased acetonuria occurred during pregnancy in 3 of 39 cases, all with living fetuses. Scholten tried to bring the acidosis of pregnancy in line with the prevailing theory of origin of acetone from proteins during carbohydrate starvation, and in 9 cases he administered 100 to 300 gm. of sugar. In 6 acetonuria promptly disappeared, while in the other 3 the women vomited the sugar. Stolz found acetonuria more common in the puerperium than earlier in gestation (38 to 50 per cent.), more common in multiparæ than in first and second pregnancies. It was not favored by lactation. He thought the acetone was derived from the metabolism of body fats and was in some way connected with the resorption of colostrum. It is remarkable that these observers failed to emphasize the toxic element which must have been present in many of their cases. Yet Waldvogel, the chief exponent of the theory of origin of all acidosis from carbohydrate starvation, detected certain discrepancies between the acetonuria of pregnancy and that of pure malnutrition.

The autotoxic nature of the disorders of pregnancy accompanied by acidosis was virtually proved by the observations of Lindemann and Bouffe St. Blaise, but the close relation between all these specific manifestations was first shown by Stone and by the writer of this paper in 1903-4. At that time we had found high ammonia ratios in the urine in pernicious vomiting, indicating severe acidosis, but finding no constant relation between the acidosis and the severity of toxic symptoms it became necessary to look to other features of metabolism for a clue to the nature of the intoxication.

Meantime, Zweifel reported an extensive study of the urinary sulphur in eclampsia, concluding that this disease consists in a remarkable deficiency in the oxidative capacity of the organism, and attributing the toxic symptoms chiefly to sarcolactic acid. According to this view, eclampsia falls in that group of acidoses which is antagonistic in origin to that due to the acetone compounds.

Williams has contributed important observations on the ammonia excretion in pernicious vomiting, dividing the cases into two groups those with high ammonia, which he recognizes as toxic, and those with low ammonia, which he regards as neurotic.

In a study with Wolf of the clinical symptoms, pathologic anatomy, and urinary chemistry of the toxemia of pregnancy, we drew the con-

clusion that pernicious vomiting, acute yellow atrophy and eclampsia are closely related conditions, connected by transitional cases, and consisting essentially in a disorder of nitrogenous metabolism involving disturbances of several processes, including probably defective desamidation. From the results of this work the routine study of the nitrogen partition in the urine in pregnancy was recommended, partly as a reliable guide to the gravity of the disease, but more urgently as a basis for prophylactic treatment by general hygiene and carefully adjusted diet. Although we found acetone compounds in many cases and recognized the significance of ammonia as a measure of acidosis, we were unable to regard the disease as essentially an acid intoxication, since these signs were missing in many very severe cases of all types, while the low urea and high amido-acid nitrogen in such cases suggested the theory of defective desamidation.

Quantitative estimation of the acetone compounds in the toxemia of pregnancy are not available, but from the ammonia ratios reported by Stone, Williams, Edgar, Ewing and Wolf, in pernicious vomiting, and by Zangemeister and Zweifel in eclampsia, it is evident that the acidosis is often severe. In one of our cases after two weeks vomiting the total ammonia nitrogen was to 1.78 gm. (14.2 per cent.); and in another case, that of a very fat woman with moderately severe symptoms, the ammonia nitrogen was 43 per cent. It is especially in the acute cases in the early months that high ammonia ratios occur. No uniform rule can be established, however, owing to the complexity of factors influencing ammonia excretion. We have seen fatal cases with normal ammonia, and are now observing a patient whose ammonia ratio for some months has run between 10 and 15 per cent. in spite of full carbohydrate diet. This patient was finally delivered of a healthy infant, after which the urine promptly became normal.

Recently a remarkable case of pernicious vomiting came under our observation at Bellevue Hospital through the kindness of Dr. Cyrus J. Strong. This patient, a well-nourished teripara, had taken little food for some weeks on account of persistent vomiting. Her condition did not appear to be critical, the chief symptoms being muscular weakness, mental dulness, and vomiting. The pulse was 80 to 100 and of good force. The accompanying table of urine analyses is furnished by my colleagues, Drs. Wolff and Shaffer.

On July 8 abortion was recommended, the patient was transferred to another service, and no further analyses were obtained. Instead of operation, moral suasion was employed with much success, as the patient stopped vomiting and retained some food. On July 14 she was delivered of a macerated four months fetus. Vomiting recurred severely and the

patient sank into a state of great weakness, mental dulness, delirium ending in coma and death, July 20. There was no autopsy.

In this case the remarkable ammonia nitrogen ratio of 75 per cent. (total 2.47 gm.) was reached and urea disappeared entirely from the urine of this day. On account of the very low nitrogen output the chemical diagnosis must be chronic starvation with acidosis, but clinically the termination of the disease took the form of pernicious vomiting of pregnancy with acute yellow atrophy of the liver.

In many of our cases, however, the ammonia totals and ratios are normal or subnormal, although the symptoms are severe or even fatal (cf. Cases 10, 12, 16-19, Ewing and Wolf). Hence, acidosis is not a constant and can not be an essential feature in all stages of the toxemia of pregnancy.

In eclampsia the ammonia ratios of Zangemeister and Zweifel, as well as our own, run below 20 per cent., while the total ammonia nitrogen does not indicate the existence of a severe grade of acidosis, and the reactions for acetone compounds are moderate.

Zweifel believes that eclampsia is an intoxication by lactic acid or its salts, but the amounts of this acid which he finds in the blood and urine are comparable to those found in other quite different conditions, while the known physiology of lactic acid does not favor the belief that it is the cause of eclamptic seizures. Dreyfuss in a recent study of eclampsia has pointed out these physiologic relations and concluded that in eclampsia lactic acid results from excessive muscular exertion, dyspnea, and disturbance of the liver.

That the specific toxemia of pregnancy is an autointoxication is amply proved, since its fulminant forms are the most violent occurring in the human subject; and it is almost equally clear that acid intoxication is a subordinate factor, although possibly affecting some cases, but the part played by starvation in this disease is not easily determined.

In the case here reported and in Case 12 of Ewing and Wolf's series the influence of prolonged starvation seems evident. But more rapid cases of the same type may be fatal in a few days, and if these are the result of starvation, then in this class of patients the essentially toxic character which starvation may sometimes assume becomes emphasized to a remarkable degree. Von Noorden seems to believe, and his pupil, Satta, actively maintains, that the condition in fasting is essentially toxic with progressive injury to the body cells, and such is the conclusion reached in the present section on this topic.

It has been objected to the use of the nitrogen partition as a clinical guide in the toxemia of pregnancy, that it shows only the influence of

URINARY ANALYSES IN A CASE OF TOXEMIA OF PREGNANCY.

Date.	No.	Volume of Urine, c.c.	Albumen.	Titrated Acidity. 100 c.c. = n c.c. — 10	Total Nitrogen, gm.	Gross Urea Nitrogen		NH_3 Nitrogen		Net Urea Nitrogen		Creatinin Nitrogen		Creatin Nitrogen		Uric Acid Nitrogen		Rest Nitrogen		Remarks.
						gm.	%	gm.	%	gm.	%	gm.	%	gm.	%	gm.	%	gm.	%	
6-11	...	770	+	slight acid.	3.58	2.77	77.5	1.82	50.9	0.95	26.6	0.11	3.1	0.12	3.4	0.06	1.7	0.52	14.5	Vomits frequently. Dull.
6-18	...	760	..	neutral.	2.44	1.57	64.4	0.99	40.6	0.58	23.8	0.19	7.8	0.08	3.3	0.046	1.9	0.13	5.3	Pulse 90-100.
6-20	173	1140	slight.	5.6	3.33	2.43	72.8	1.77	53.1	0.656	19.7	0.265	8.0	0.023	0.7	0.048	1.4	0.57	17.1	
6-21	176	1025	trace.	10.4	3.34	2.41	72.2	1.79	53.6	0.62	18.5	0.268	8.0	0.024	0.7	0.04	1.2	0.60	18.0	
6-22	177	1440	slight.	12.	3.69	2.84	76.5	2.31	62.7	0.53	13.8	0.28	7.6	0.04	1.1	0.09	2.4	0.44	12.0	
6-23	178	1175	slight.	15.5	3.33	2.56	77.0	2.47	74.2	0.09	2.8	0.21	6.4	0.06	1.9	0.10	2.9	0.40	12.0	
6-24	179	1410	slight.	6.4	2.75	2.17	75.0	2.17	75.0	.0	.0	0.193	7.0	0.045	1.7	0.103	3.7	0.35	12.7	
6-25	180	1880	+	5.6	3.38	2.64	78.3	2.13	62.5	0.51	15.8	0.167	5.0	0.12	3.6	0.13	3.9	0.32	9.5	
6-26	181	1300	+	6.4	2.58	2.03	78.7	1.75	67.8	0.28	10.9	0.184	7.1	0.03	1.2	0.066	2.5	0.27	10.5	
6-29	184	270	+	neutral.	1.28	0.77	59.9	0.354	27.8	0.42	32.1	0.17	13.3	0.043	3.4	0.016	1.3	0.28	22.7	No chloroform — perhaps slight decomposition June 28: Fluid foods stopped, solid foods given. Uric acid uncertain. Double strabismus. Partial blindness.
6-30	185	825	+	slight acid.	4.05	2.86	70.6	0.71	17.5	2.15	53.1	0.33	8.1	0.06	1.6	0.17	4.1	0.63	15.6	Irrational.
7- 1	186	850	+	slight acid.	4.45	3.63	81.5	0.49	11.0	3.14	70.5	0.223	5.0	0.05	1.2	0.104	2.3	0.37	9.0	
7- 2	188	290	+	slight acid.	1.81	1.50	82.9	0.16	8.9	1.34	74.0	0.079	4.4	0.026	1.4	0.031	1.7	0.17	9.4	
7- 3	189	435	+	slight acid.	3.43	2.78	81.3	0.30	8.7	2.48	72.8	0.157	4.6	0.011	0.3	0.053	1.5	0.41	12.0	Diacetic acid very marked. Less nervous. Sat up in chair. July 10: Delirious.
7- 8	199	220	+	acid.	2.66	2.06	77.5	0.14	5.3	1.92	72.2	0.167	6.3	0.034	1.3	0.062	2.3	0.34	12.7	Patient received 150 gm. sugar. July 14: Abortion. Macerated fetus.
7-11	201	455	+	acid.	4.5	3.30	73.3	0.255	5.7	3.04	67.7	0.318	7.1	0.085	1.9	0.14	3.1	0.66	14.7	Vomiting recurred. Died July 20.

starvation. According to the present view, however, its significance is not thereby reduced, since it would then indicate the progress of a type of starvation which may prove rapidly fatal. But it is difficult to accept the peculiar symptoms of pernicious vomiting as those of starvation, and the urinary analyses are in some important respects quite different.

Among the chief distinctions are the inconstancy of acidosis, the occurrence of high total ammonia without acidosis, and the high proportion of amido-acid nitrogen. These signs point to a deficiency of urea forming function, possibly to defective desamidation, leading to degenerative changes in the liver and other organs and to a fatal collapse of the chemical control of the organism. The clinical condition shows a striking resemblance to that described by Minkowski after extirpation of the liver or following the Eck fistula. According to this view, which assumes the existence of injured organ cells, there is room for the belief that an excessive neurotic element or severe acidosis or indol poisoning, may stamp certain cases with peculiar features. It is probable that many of the fatalities in this case are due to delayed chloroform poisoning. Yet obstetricians continue to use this anesthetic freely.

It is not an infrequent experience to find that persistent vomiting in the earlier months of pregnancy is followed after an interval by albuminuria and later by the pre-eclampsic state of Edgar, or by eclampsia with moderate or pronounced nephritis. The observations on acidosis threw some light on this sequence of events. In many experimental forms of acid intoxication beginning with the discovery of Kulz's coma casts, which I have observed in hydrochloric acid poisoning, in the experiments on the toxicity of acetone compounds, and in many clinical studies, it is apparent that prolonged acidosis tends to set up nephritis. Diabetes for special reasons is a partial exception to this rule, and yet it is extremely rare for diabetes to prove fatal without active nephritis. Of the mechanism of this relation little is known, but the fact that it exists is sufficiently attested and should encourage efforts to combat acidosis whenever it appears, especially in the toxemia of pregnancy.

Cyclic Vomiting.

There are several types of periodical vomiting in children and in one of these acidosis is prominent and acid intoxication has been urged as the essential pathogenic factor. There is a purely neurotic vomiting described by Leyden, Reymond and others; a second type, referable to errors of diet and relieved by the vomiting and purging, is described in this connection by Fenwick, Symes, and Gee, and it is obvious that any of the bacterial causes of gastritis in children may act periodically.

Characteristic cyclic vomiting occurs only in children, usually in neurotic subjects, at frequent intervals, not connected with dietetic errors, and not relieved by vomiting or purging. The vomiting is very severe, and the vomitus may contain mucus, bile, blood, acetone, and indol, and is accompanied by great prostration, thirst and emaciation, but not by pain. There is restlessness, headache, and there may be delirium, convulsions and coma. The temperature may be subnormal or rise to 110 F. Respiration is rapid, sighing and irregular. The attack usually lasts but a few days, but may be continued for two weeks or prove fatal in forty-eight hours. Recurrence is common. The urine before the attack may contain much indican, increased uric acid, and some acetone; during the attacks it is diminished with less indican or uric acid, more acetone compounds, and often with albumin, casts, or blood.

Several theories of the nature of this disease have been maintained. The theory of a gastric neurosis applies to one predisposing element. Rachford believes that the malady is a lithemic condition allied to migraine, and in one of his patients the attacks changed to migraine as the patient grew older. Excess of uric acid has been found in the urine by Pepper, Holt, Griffith, Valagusa, and Comby, and appears to be a very constant feature of the disease.

The acetone compounds have been found in the urine and breath by Marcy, Edsall, Marfan and others, and Edsall has urged that the disease is a form of acid intoxication.

Several observations favor this hypothesis. Although quantitative estimations of the acetone compounds have not been made, the reactions in the urine have often been pronounced, and the breath may give a strong odor of acetone. Acetone may occur in the urine before the attack (Marfan). It may appear in the vomitus, suggesting that the vomiting is an eliminative mechanism. Edsall states that the respiratory disturbance resembles that of diabetic coma and he strongly recommends alkali therapy, while he and Pierson assert that they have cured some and prevented other attacks by this method. On the other hand, the acetone compounds do not appear to be present in quantities sufficient to account for the severe symptoms, and their toxicity is slight. These substances occur very readily in children not presenting the symptoms of cyclic vomiting (Baginsky, Langmead). The resemblance of the dyspnea to that of acid coma has not impressed the majority of observers. The good effects of alkali therapy here, as in diabetic coma, may be referable to other actions than the neutralization of acids (Shaw and

Tribe), while this treatment may fail and other forms of treatment may be equally or more effective (Griffith, Shaw, Tribe and Marfan).

The researches of Howland and Richards have gone far toward elucidating the nature of cyclic vomiting in children. In a series of cases they found acetone compounds and lactic acid, a rise in the ratio of neutral to oxidized sulphur, and heavy indicanuria, which diminishes during the attack. All these urinary signs they interpret as evidence of deficient oxidation by the body cells. They argue that the rise in uric acid must represent endogenous nucleo-proteid metabolism since exogenous sources of uric acid are reduced with the scanty diet of the patients.

The appearance of acetone compounds and lactic acid can not be due, they think, to lack of carbohydrates, since the symptoms appear too soon—three to four hours after a full diet— and must be referable to failure to burn carbohydrates and fats properly. They attach great importance to the presence of much indol, phenol and skatol in the urine. Before the attack indicanuria is greatly increased, indicating increased intestinal putrefaction. While indol is comparatively non-toxic in the healthy organism, they show that when the animal's detoxicating power is reduced by slight poisoning with potassium cyanid or chloroform, or by asphyxia, indol becomes extremely toxic, producing vomiting, hematomesis, blindness, convulsions, and death. In dogs thus poisoned by potassium cyanid 0.25 to 0.5 gm. of indol produced very marked symptoms, although 18 gm. of indol have been found innocuous in healthy animals. In their poisoned dogs the excretion of indol as indican was delayed and less was found in the urine than with normal dogs. This observation indicates that the amount of indican in the urine is determined not merely by the amount of indol absorbed, but by the capacity of the organism to combine with sulphuric acid and excrete it as indican. I have repeatedly found that indican decreases or completely disappears in the urine, during attacks of migraine, in patients who excrete large quantities before and after the attack.

Howland and Richards conclude that cyclic vomiting results from deficient oxidation brought about in predisposed subjects by nervous disturbance, and leading to failure to detoxicate products of intestinal putrefaction, and of internal metabolism.

That the subjects of cyclic vomiting suffer from severe autointoxication is indicated not only by the urinary signs, but by the extensive granular and fatty degeneration of the liver and kidneys recorded in the autopsies of Griffith and Marcy, and observed in many other conditions accompanied by acidosis.

There is also good reason to believe that indol is a prominent toxic agent in this disease. Since similar evidence has not been obtained of the toxic action of acid products of metabolism, and since the quantity of these acid products excreted has not been determined, and since the symptoms and lesions of the disease are not those of the most probable manifestations of simple acidosis, I think one can not endorse the view that cyclic vomiting is a form of acid intoxication, with extensive loss of tissue alkalies. It appears to be rather a complex disturbance of metabolism occurring in neurotic and predisposed subjects, in which rapid burning of body fats, defective function of the liver, and poisoning by intestinal putrefactive products are combined. Studies on the nitrogen partition, especially the ammonia and residual nitrogen, quantitative estimations of the acetone compounds, of lactic acid, and of the alkalescence of the blood are needed in this field, and are essential before one can estimate the relative importance of these factors.

Acidosis After Anesthesia.

Becker, who first studied the acidosis following anesthesia, found acetonuria in two-thirds of all subjects. It was more marked in women than in men and most pronounced in children, appearing in the first or second portion of urine passed, and lasting eight or nine days. It was uninfluenced by the length or character of the narcosis, and occurred after one minute's inhalation of bromether. Abram found acetone in all of 25 cases, but in 9 Legal's reaction appeared only in the distillate. Ether seemed to be less effective than chloroform. Waldvogel observed acetonuria in three-fourths of fifty cases, demonstrating diacetic and beta-oxybutyric acids in thirteen cases on the first day. The highest amount of beta-oxybutyric acid observed was 2.5 gm. in eighteen hours. In two cases acetone compounds were at first absent and considerable glycosuria occurred.

The fatal effects of anesthesia in diabetes, of which Becker collected thirteen cases, seemed thus to receive a partial explanation, since it was early seen that existing acetonuria was made worse by the anesthetic. A direct toxic origin of this form of acetonuria seemed obvious, but Waldvogel attempted to prove that it was chiefly referable to the withdrawal of food in the preparation for the anesthetic, and to the subsequent vomiting. In several cases he was able to show that acetonuria did not appear if the patient was anesthetized on a full stomach and did not vomit after recovery. Yet, since children of 6 to 9 years, whom he allowed to fast for seven hours, failed to show increased acetonuria, and since the influence of carbohydrate in relieving the acidosis from chloro-

form was much slower than in simple starvation, Waldvogel was forced to conclude that a direct toxic action of the anesthetic was an important factor in producing the acidosis. Baldwin, in a study of forty-one cases, gave 25 to 50 gm. of glucose to six patients without evident effect on the acetonuria.

It has been shown in dogs (Marum) and assumed for man that acetone does not appear in the urine until the glycogen of the liver has been consumed and no more carbohydrate is available. But the immediate appearance of acetone after anesthesia shows that this course of physiologic events is not invariable and points to a direct interference with carbohydrate consumption exerted by the chloroform. The very early appearance of fatty degeneration of the liver after chloroform narcosis is of similar import.

It has long been known that the dangers of chloroform, and, to a less extent, of ether are not exhausted in its immediate effects. In recent years attention has frequently been drawn to the occurrence, chiefly in children, of a type of delayed chloroform poisoning, in which the patient after more or less complete recovery from the anesthetic, after a few hours or days, fell into a state of fatal intoxication marked by vomiting, acetonuria, acetone breath, extreme prostration, albuminuria, cyanosis, nervous excitement, followed by delirium, coma, and death.

Guthrie, in 1894 and again 1903, emphasized the frequency and importance of this peculiar intoxication, regarding it as a result of chloroform poisoning added to a pre-existing fatty degeneration of the liver. So pronounced was this change in the liver and so much did the symptoms resemble those of acute yellow atrophy, that he was inclined to believe that the two conditions were closely related, and he referred to cases of acute yellow atrophy following operation collected by Schenck and by Ballin in support of this view.

That these cases may be accompanied by marked acidosis was shown by Brewer in 1902 in a remrakable case fatal three days after operation for acute appendicitis, in which considerable amounts of acetone and diacetic acid were found.

Bracket, Stone and Low, and later Kelly, have reported a series of cases of this general type occurring in young children at the Boston City Hospital. The patients were, as a rule, rather poor subjects for surgical treatment, some suffering from infantile paralysis or intestinal obstruction; one seems to have been subject to cyclic vomiting, and all exhibited a neurotic tendency which was not improved by hospital surroundings. In six cases the symptoms developed without operation, and one of these was fatal, but most of the severe cases occurred after anes-

thesia by ether. The grade of acidosis was probably not severe, as Joslin found only 0.142 gm. of acetone in the urine from a patient dying twenty hours after operation. At autopsy extensive fatty degeneration of the liver and kidneys was found. Treatment by fat-free diet and bicarbonate of soda seemed to have good effects in some cases, but not in others, and no better than those following salt infusion. Later Stiles and McDonald (1904) presented a full clinical and pathologic picture of delayed chloroform poisoning, assuming that it is a form of poisoning by acetone compounds; and a similar conclusion was reached by Carmichael and Beattie, the latter authors excluding constitutio lymphatica in their cases. Bevan and Favill, in a full review of the subject, cite several cases of acute yellow atrophy of the liver following anesthesia, in which group their own case seems to fall. They strongly emphasize the dangers of chloroform anesthesia in predisposed subjects and conclude that the chloroform directly injures the liver cells while the acidosis is a secondary and comparatively unimportant feature of the intoxication.

There is no doubt that the cases included in the foregoing reports represent a heterogeneous group of conditions, of which acidosis is a more or less constant feature. None of the authors brings forward satisfactory evidence that acid intoxication of any form is a prominent factor in the symptoms, but the occurrence of this type of fatal intoxication is not only of great practical importance, but has rather decisive bearing on the general question of the significance of acidosis and acid intoxication. These cases demonstrate a highly toxic condition with extensive injury to organ cells, in which there is marked acidosis, and thus they emphasize the toxic element in some other forms of acidosis. They leave undetermined, as it appears to me, what part, if any, the acidosis plays in the symptoms and fatal issue, but many of the cases suggest that the sudden burning of body fats when the liver is seriously injured is a process that may become dangerous to life. Yet the observations are quite inadequate to prove the real character of the underlying disturbance of metabolism.

In some cases of delayed chloroform poisoning and of acute appendicitis fatal after operation I have found very low urea, rather high ammonia and excessive residual nitrogen, suggesting that this is a condition in which the urea-forming and other functions of the liver are fatally deficient. Further systematic urinary analyses are essential for the correct interpretation of this group of cases. There are many reasons for supposing that it will be found to follow the prototype of the intoxication following extirpation of the liver, or the Eck fistula.

From the practical side the observations on delayed chloroform intoxication are of much value, since they serve to define an important

particular in which certain subjects may be recognized as bad surgical risks. It is the consensus of opinion, from which only Carmichael and Beattie dissent, that the intoxication occurs only in predisposed subjects of nervous temperament, and weakened by fatty alterations of the liver, and one need not assume the existence of fatty degeneration in order to explain the weakened state of the organism. In view of the many unfavorable factors, as youth, previous chronic malnutrition or disease, and anesthesia, which seem to concur in producing the fatal result, it may be necessary to reopen, for this group of cases, the question of the direct toxicity of salts of the fatty acids. In any event attention may be called to this group of cases as a most favorable field for the study of problems relating to acidosis.

Miscellaneous Clinical Types of Acidosis.

There remain for consideration several clinical conditions in which von Jaksch believed he could recognize the effects of acetonemia, but in which later investigations have shown that the acidosis is the result and probably not the cause of symptoms and that the acetonuria is not the result of absorption from the intestinal tract, but the sequel of carbohydrate starvation. Under the title of "acetonuria from digestive disturbances" have been described a heterogeneous class of cases, marked by vomiting and diarrhea, acetonuria, and a variety of nervous symptoms which the older authors were disposed to refer to acetonemia. In this field it is extremely difficult to attempt any classification or to trace the influence of many factors concerned, but several somewhat coherent groups of cases may be recognized.

One of these has been separately considered as "cyclic vomiting of children." In addition to this somewhat special recurrent type, the ordinary gastro-enteritis of infants has been found associated with the presence in the urine of all the acetone compounds, and the nervous symptoms of many of the cases suggests a relation to acetonuria (Vergely, Schrack, Engel). In the extensive reports of von Jaksch and of Lorenz one finds many cases of digestive acetonuria with epileptiform convulsions, which, on inspection, one must attribute to a great many different diseases, as eclampsia, uremia, lead poisoning, hydrocephalus, chronic meningitis, etc.

Cassaet has isolated highly toxic alkaloids from the stools of such patients showing much acidosis, and it is much more reasonable to attribute the symptoms to this class of substances, rather than to any form of acidosis.

COMA DYSPEPTICUM.

"Coma dyspepticum" is a term applied to a group of symptoms described by Litten and observed by him in five cases. After a short period of dyspepsia referable to errors of diet the patients began to suffer from prostration, chilliness, anorexia, thirst, constipation or diarrhea, and occasional vomiting soon followed by pronounced nervous disturbance, headache, restlessness and excitement varying with depression. Later a pronounced odor of acetone on the breath, and marked ferric chlorid reaction in the urine appeared, and the patients became dull, apathetic, and semicomatose. After two or three days recovery followed with disappearance of the acetone. Although glycosuria was absent, Litten regarded this condition as related to diabetic coma. The relation of acetonuria to coma dyspepticum appears never to have been determined.

ASTHMA ACETONICUM, HYSTERIA AND OBSTIPATION.

The "asthma acetonicum" of Pawinski has long been recognized as uremic vomiting and nephritic dyspnea.

In hysteria with vomiting high grades of acetonuria may obviously be attributed to starvation, but the process may nevertheless be toxic. In cases of obstipation very strong acetone reactions have been obtained in both urine and feces, but nervous symptoms such as might be attributed to acetonemia are inconstant or absent (cf. Lorenz, case 37).

In all the above groups the lack of relation between the nervous symptoms and the grade of acetonuria, the appearance of acetone after and not before the onset of symptoms, and the existence of many other probable sources of nervous symptoms, strengthen the belief that the acetonuria is the result chiefly of carbohydrate starvation and that the acidosis is usually a secondary and negligible factor.

The possibility that acetone compounds absorbed from the intestine contribute to the symptoms has been frequently mentioned (Vergeley), but is not strengthened by the relatively small amounts of these substances so far demonstrated in the gastrointestinal contents (Savelieff, Baginsky), while any possible toxicity of the fatty acid derivatives is very far below that of indol and other putrefactive products. The fatty stools of milk-fed infants have perhaps not been sufficiently studied from this point of view. Excess of fat in the food increases acetonuria, and carbohydrates diminish intestinal putrefaction (Hirschler). Hence, there is perhaps still some reason to believe that in some cases acetonuria in digestive disturbances may be partly referable to intestinal absorption.

ACIDOSIS OF CANCER.

Among the types of acetonuria described by von Jaksch was that occurring in the late stages of gastric carcinoma in certain well-nourished patients who suffered from severe vomiting. Some of these patients passed into coma and it was pointed out by Riess and Litten that sufferers from this coma often exhibited the "grosse Atmung" of Kussmaul's dyspneic coma of diabetes. Von Jaksch stated that these patients were not always suffering from starvation; that the acetonuria might appear unexpectedly in the disease; and that its appearance sometimes marked the onset of a severe type of cancerous cachexia.

In two cases of esophageal and gastric carcinoma with typical Kussmaul's coma, Klemperer demonstrated a daily loss of nitrogen on balance of 5 to 9 gm., indicating toxic destruction of tissues, and there were also small amounts of beta-oxybutyric acid in the urine. Klemperer concludes that in both cancer and diabetes the coma, the destruction of tissues, and the acidosis, are the result of a general toxic process, but that in neither case does the acidosis produce the coma. F. Müller had previously shown that nearly all cases of cancer lose nitrogen on balance, and Waldvogel suggests that destruction of protein tissues may very well be associated with toxic destruction of fats and thus give rise to acidosis.

It is evident that in most cases of cancer coma the patients are undernourished or starving and that inanition is the chief factor in this form of acidosis. Von Noorden finds that acetonuria is absent in cancer when the nutrition is good and begins to appear when the destruction of proteid tissues becomes evident. Waldvogel failed to find increased acetonuria in several advanced cases of cancer in which the patients were well fed, and Hirschfeld relieved the acidosis in such cases by giving sugar. It nevertheless appears possible that the extensive burning of body fats and proteins in a cachectic organism may be one of the factors responsible for some of the sudden terminations of carcinoma.

ACIDOSIS IN PSYCHOSIS.

The prominence of nervous symptoms lends special interest to the acetonuria of psychoses, yet in this field there has never been a strong tendency to refer the nervous symptoms to acetone poisoning or acid intoxication. Tuczek first observed diacetic acid in the urine in psychoses when the patients were fasting, while von Jaksch was unable to prove that acetonuria was at all constant when such patients were well nourished. Jauregg, however, asserted that he was able to detect peculiar characteristics in certain psychoses which showed a definite relation to acetonuria, which he regarded as of intestinal origin, and for which he recommended

intestinal antisepsis. That no such relation exists in melancholia, mania and paresis was fully shown by de Boeck and Slosse, who found acetonuria in such cases only when the patients were inadequately fed. In epilepsy acetone may appear after severe seizures, together with lactic acid (Luthje, Araki).

FEBRILE ACETONURIA.

In the extensive literature on this topic one finds further illustration of the rules governing the occurrence of acetone compounds, but no indication that acidosis is a necessary or significant feature of the febrile process or that it contributes to the common symptoms of infectious diseases. Von Jaksch found that it usually—but not always—bore a relation to the height of the fever, but it was inconstant in occurrence, reaching a grade (maximum 500 mg.) considerably lower than that of starvation or diabetes and without definite relation to prognosis. In children, as usual, it becomes most pronounced. In pneumonia of children Pfaundler observed acetonuria in twenty-nine of fifty cases. In adults Engel, in five cases, saw moderate but variable increase. Lambert and Wolf, in a series of cases, report rather pronounced increase in the total ammonia, indicating considerable acidosis.

In typhoid fever the acetonuria is more marked and constant but by no means invariable. Engel found a maximum of 226 mg. acetone in seven cases. In two of these acetonuria and diarrhea were absent. Fraenckel frequently saw initial acetonuria disappear when a moderate amount of food was given. As judged by the ammonia nitrogen in a series of cases I found typhoid fever to be strikingly free from acidosis. Even with an antemortem fall in net urea the ammonia did not rise above 10 per cent. and usually remained within normal limits. The occurrence of very toxic cases of typhoid fever and of terminations in acute yellow atrophy show that this disease may be complicated by severe types of autointoxication (Ewing), and among the factors concerned may perhaps be found severe acidosis from burning of body fats and decline of hepatic function.

In measles and scarlet fever Kulz early detected beta-oxybutyric acid. In a case of scarlatina in a woman of 31 years Litten describes a typical case of Kussmaul's coma with marked acetonuria which disappeared with relief of the coma.

That the element of partial starvation is concerned in febrile acetonuria is conceded by all observers, but many have expressed the opinion that a toxic destruction of tissues is also to be considered as a factor. Botazzi and Orefici show that in diphtheria the acetonuria reaches its maximum at the time of greatest loss of nitrogen balance and

is promptly reduced by antitoxin. Blumenthal found in streptococcus infection a special tendency to cause acetonuria. The increased acidosis observed in diabetics suffering from febrile disease points to a toxic process (Ebstein, Engel). The carbon dioxid content of the blood is greatly reduced (Loewy, Münzer, Meyer) and the titratable alkali is much diminished, 35 mg. sodium hydrate (von Jaksch).

After a full consideration of the complex conditions in which febrile acetonuria appears, Waldvogel concludes that it results from destruction of fats due to inanition and cell injury and is influenced by the nature of the poison, the location of the disease focus, the instability of the fat tissues and individual peculiarities.

ACETONURIA FROM POISONING BY DRUGS.

Varying grades of acetonuria are observed after administration of many drugs, as phosphorus, arsenic, lead, phloridzin, antipyrin, pyrodin, morphin, atropin, curare, carbon monoxid and sulphuric acid. In the action of all these there appears to be an influence of starvation, but also a more prominent toxic effect. In some instances the toxic influence seems to act through deficient oxidation, as with the hematoxic agents, pyrodin, carbon monoxid and with phosphorus. With all of these the acetonuria appears very promptly, may be increased by larger doses of the drug, and as a rule is comparatively uninfluenced by any carbohydrate that may be given (Walko, Boeri, Waldvogel). In phosphorus poisoning acidosis appears in the first hours but is not always proportional to the severity of the intoxication or to the glycosuria. Schwarz found in breath and urine 0.61 mg. acetone on the third day, 0.56 gm. on the second day, mostly in the breath, while a larger amount, 1.31 gm., was determined on the second day of a very mild case. Diacetic acid was commonly present, but beta-oxybutyric acid was never detected. The acidosis was not influenced by carbohydrate feeding. Münzer found the ammonia nitrogen regularly increased from 10 to 22 per cent. (0.5 to 2.2 gm). He regarded the increased ammonia as solely the result of acidosis in which sarcolactic acid was prominent, and since administration of alkalies reduced the ammonia without affecting the symptoms, he held that poisoning by ammonia salts did not occur. He usually detected acetone in marked amounts.

The exact sources of the acidosis of phosphorus poisoning have not been finally determined. It is evident that the acetone compounds are insufficient to explain it, and most authors consider lactic, phosphoric and sulphuric acids as the chief sources. Münzer calculated that the excess of urinary ammonia could all be referred to lactic, phosphoric,

sulphuric and oxy-acids derived from increased destruction of proteins. Yet the extreme disturbance of the fat depots of the body, the splitting off of fatty acids and lecithin in the organ cells (Mavraki, Saxl), and the interference with several normal metabolic processes, give abundant opportunity for the formation of acetone compounds, which Waldvogel and others believe are prominently concerned in the acidosis of phosphorus poisoning.

Phloridzin produces acidosis in all animals, least promptly in the dog. According to Baer phloridzinized dogs in nitrogen equilibrium show no acidosis; acidosis appears only when the glycogen of the liver has been exhausted and proteins and fats are being called on for energy. The demonstration of this rule governing the appearance of acetonuria has thrown much light on the mechanism of action of the toxic causes of acidosis and is further evidence of the essential relation of carbohydrate combustion to these forms of acidosis.

With the remaining drugs which induce acetonuria the grade of acidosis is moderate, and the factors of malnutrition and special toxic action are variously combined, but in none of them do the data seem to deserve special consideration at this time from the clinical or theoretical side.

THE SIGNIFICANCE OF THE PATHOLOGIC ANATOMY OF ACIDOSIS AND A CLASSIFICATION OF ACIDOSES BASED CHIEFLY THEREON.

Pathologic anatomy has been given a very scant hearing in the debatable ground of acid intoxication, but it has seemed to me that more important clues might be obtained from this field than have yet been secured. Indeed, notwithstanding all that may be said about the lack of relation between histologic structure and functional capacity of organs, I think it will eventually be proved a grave error to associate together such conditions as diabetic acidosis, in which the liver is practically normal, and that of delayed chloroform poisoning, in which this important organ may be nearly destroyed.

In the two experimental prototypes of acidosis, Walter's acid poisoning and Minkowski's extirpation of the liver, the anatomic conditions are entirely different. In poisoning by hydrochloric acid there are no prominent anatomic lesions, while after various procedures for eliminating the function of the liver, as the Eck fistula or injections of acid into the bile ducts, this organ becomes completely necrotic. Reviewing the clinical types of acidosis, especially their pathologic anatomy, it appears possible to separate them into two rather distinct classes resembling the two experimental types above mentioned. This division may be based mainly, in one, on the absence of anatomic changes in the viscera and

presence of excessive amounts of acetone compounds in the urine, and, for the other, on the occurrence of marked degenerative changes in the organs and the presence of much lactic acid. In the former case acids are produced in excess and ammonia is diverted to neutralize them. Here the formation of acids is the primary event, while the diversion of ammonia is a compensatory process. In the latter type ammonia appears in excess, not to neutralize acids but from failure of its synthesis into urea, while the acids result partly from failure of urea formation but also from other factors in the disease. Whatever their source, some of these acids unite with ammonia, but this fact does not prove that the process is merely compensatory.

Classification of Acidoses.

Group 1.—Type: Hydrochloric Acid Poisoning.

Pathologic Anatomy: No prominent lesions.
Pathologic Chemistry: Acetone bodies chiefly present; ammonia proportional to these acids; amido-acids slightly increased.
Clinical Forms: Diabetic coma; Kussmaul's coma; starvation.

Group 2.—Type: Extirpation of Liver, Eck Fistula.

Pathologic Anatomy: Extensive fatty degeneration.
Pathologic Chemistry: Lactic acid abundant; acetone bodies less prominent; ammonia in excess of fatty acids; amido-acid nitrogen much increased; glucose frequently present.
Clinical Forms: Phosphorus poisoning; pernicious vomiting of pregnancy; acute yellow atrophy; eclampsia; delayed chloroform poisoning; cyclic vomiting.

The general facts on which this division is based are contained in previous discussions, but some further grounds may be briefly reviewed in its support.

In diabetic coma the urinary chemistry and the clinical symptoms obviously accord with the type. The liver in diabetic coma varies extremely, but in uncomplicated cases usually shows a striking absence of fatty degeneration. In Naunyn's series of thirty autopsies fatty liver was found but once and that in a case of spontaneous diabetes in a dog. Minkowski has collected many reports, most of which indicate that fatty livers are comparatively rare in diabetic coma. Fatty liver occurred but once, and in an alcoholic subject, among eleven cases of diabetic coma which I have recently collected. Therefore I conclude that fatty liver is not essential in diabetic coma in man, and when it occurs may usually be referred to complications.

In starvation the organs undergo a process of simple atrophy, in which fatty changes are not prominent (Morpurgo). In the earlier stages of hunger in dogs there may be a moderate deposit of fine fat

granules in many gland cells, but these disappear in the late stages (Nicolaides). Extreme grades of fatty degeneration are apparently quite unknown in simple starvation. In the urine of starvation acidosis acetone compounds are abundant and lactic acid scanty.

On the other hand, all the forms of Group 2, except eclampsia, are characterized by a remarkable grade of fatty degeneration of the liver and often of other organs. In eclampsia fatty degeneration is usually not pronounced but acute degeneration or autolysis is constant, and there is reason to regard this change as of more significance than the hemorrhagic hepatitis.

In phosphorus poisoning, acute yellow atrophy, and eclampsia, lactic acid is more prominent than the acetone compounds, but in the other diseases of this group lactic acid has not been fully studied, while the presence of acetone bodies one may refer to complicating acidosis of starvation or toxic consumption of fats.

In the second group the severity of the condition is much greater than in the first. In diabetes and starvation the metabolism of fats is defective owing to lack of carbohydrate combustion, while the structure of the organs does not suffer, but in phosphorus poisoning and eclampsia the liver and other organs are severely damaged and their functions are greatly disturbed. In the first group there may be extreme acidosis without intoxication; in the other the excess of acetone compounds is slight, a more definite toxic element is present from the first, and the metabolic disorder becomes complex.

Nencki and Hahn, Denys and Stube, and Pick, attributed the symptom following destruction of the liver to poisoning by ammonium carbamate, but Lieblein concludes that excess of ammonium salts does not appear until the last stages of the intoxication and that the symptoms must be attributed to the loss of other functions of the liver. The physiologic significance of carbamic acid has not been satisfactorily determined, owing to uncertainties in the available methods (McLeod, Haskins). The relation of this acid to the urinary ammonia in dogs with Eck fistulæ is therefore uncertain.

In diabetic coma the abstraction of fixed alkalies is very probably an important factor, while in other conditions this influence appears less prominent, the alkalescence of the blood is not greatly reduced, and poisoning by ammonium salts, if we may accept the hypothesis of Hahn and Nencki, dominates the clinical picture. This hypothesis has not gained general acceptance, but there is no doubt of the extreme toxicity of ammonium salts as compared with that of the acetone bodies, and any one who compares the toxicity of these agents in animals can not

fail to be impressed by the comparative harmlessness of the acetone bodies and violent nervous and respiratory symptoms following injections ammonia salts. Mendel has recently urged the possible importance of the toxicity of ammonium salts in acidosis, and it is my belief that there is much clinical, pathologic and chemical evidence to support this view for certain diseases commonly regarded as forms of acid intoxication. I am not prepared to argue that the main symptoms of all these diseases are caused by ammonia poisoning, but only to state that the ammonia excretion in these conditions may and usually does have an entirely different significance from that attaching to it in diabetes and simple starvation.

Many transitional cases of acidosis undoubtedly occur, as the toxic element increases, as the scope of defective metabolism widens, and the disturbance becomes more complicated by visceral lesions, and it may be that the transitional and complex cases are so numerous as to destroy the significance of any attempt at classification. In the toxemia of pregnancy, delayed chloroform poisoning, and cyclic vomiting, there may be extensive burning of body fats, and several factors may combine to raise the ammonia. With Wolf, I have previously emphasized the importance of other changes in the nitrogen partition, especially of the amido-acid ratio, as a control of the ammonia and as indicating the influence of other disturbances of metabolism quite apart from the signs of acidosis.

While the typical cases of both classes seem to be quite distinct, the present subdivision can be suggested only as an hypothesis the validity of which must be determined by future investigations.

CONCLUSIONS.

In a field which presents the most varied and perplexing of clinical phenomena, in which pathologic anatomy offers uncertain guidance, and in which physiologic chemistry, while having to deal with many uncertain technical methods, encounters such problems as the alkalescence and ion concentration of the blood, the general significance of alkalies, the more complicated processes in many departments of metabolism, including the physiology of proteins, carbohydrates, and fats, as well as that of many inorganic principles of the body—in such a field it is not to be expected that positive answers can be given to the many questions that are being pressed. One must await further progress in collateral sciences before the significance of acidosis can be fully determined.

It is superfluous to urge the need of further work in all departments of this study. Prominent among the requirements seem to be the simpli-

fication of technical methods, the further elucidation of the alkalescence and acid-neutralizing function of the blood, the study of variations in the alkali content of the organs, of the quantities of acetone compounds and other acids in the blood and organs of many diseases, the toxicity of acid substances and other metabolic products when combined with pre-existing lesions of the organs, and the more complete picture of nitrogenous metabolism in diseases accompanied by acidosis.

In the pursuit of these topics it should be recognized that the significance of acetonuria and of the results of many clinical methods of urine and blood analysis is not yet clear enough to render simple qualitative tests of much value; yet the importance of work of this type, if only from an educational standpoint, should not be underestimated. At the same time it must be urged that genuine progress can be attained only by the most accurate methods of fully equipped chemical and pathologic laboratories, systematically applied in cooperation with clinicians under ideal hospital facilities.

The demands of the future need not, however, obscure the importance of the results already secured. The work on acidosis is a fundamental chapter in medical science revealing in a trustworthy manner the exact nature and degree of a disturbance of metabolism which is of widespread occurrence and of prime significance in many diseases.

In the hands of the clinician it places a means of diagnosis and an insight into the nature of disease which entirely escape the reach of former methods of clinical study.

To the pathologic anatomist it has disclosed the main factors in the pathogenesis of fatty degeneration, and has given to the much-contemned autopsy finding of fatty liver a definite, new, and lively interest. Read in terms of physiologic chemistry, acute degeneration of the liver becomes a topic of first importance to the pathologist.

From the standpoint of physiologic chemistry the results seem to show that acidosis with the presence of acetone compounds usually results from abnormal metabolism of body or food fats and to a less extent of proteins, in which defective consumption of carbohydrates is an essential factor, and excessive excretion of ammonia a purely compensatory process.

In many cases, however, there is a toxic or specific element which interferes with consumption of carbohydrates, even when these are present, and leads to a rapid and dangerous burning of body fats.

In a third group of cases the excess of ammonia excretion is not a compensatory process, but the result of disturbance of urea formation, and lactic and other acids appear in excess.

The therapeutic importance of the doctrine of acid intoxication has always been recognized and sometimes, perhaps, overestimated. It seems to be time that the idea of a fatal abstraction of alkali in diabetic coma should give place to unbiased search for other factors in this disease, some of which may be affected by treatment. It is not necessary to deny the existence of acid intoxication in order to recognize that the alkali treatment of coma has been a signal disappointment. While this treatment certaintly deserves a place in the treatment of diabetes, its place must be secondary since there is no claim that it favorably influences the essential process in the disease. The remarkable antiketogenic effect of glyconic and glutaric acids suggests a new hope in the treatment of diabetic acidosis, but I learn that this hope has already met with disappointment. This result merely emphasizes the fact that diabetic coma is something more than acid intoxication.

On the other hand, it is not necessary to know all about the origin and pathogenic relations of acidosis to see the clear indications that, whenever present, it should be combated by carefully adjusted diet, by other hygienic measures, but chiefly by prophylaxis. Here lies the great practical value of the studies of acidosis, and it would be difficult to overestimate the importance to the practitioner of a detailed knowledge of all departments of the subject, and an ability to follow up its clues, especially in administering anesthetics, in the choice and preparation of subjects for operation, in the management of pregnancy and labor, in the control of gastrointestinal diseases of children, and in the general plan of dietetics in disease.

The study of acidosis shows one thing clearly: that the feeding of the healthy man, as well as the diet of the sick, can not be left to chance, guided by appetite, or ruled by tradition, but can be safely directed only according to the laws of digestion and metabolism.

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THE INTESTINAL LESIONS CAUSED BY TRICHINELLA SPIRALIS IN RATS.*

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In a former publication[1] the lesions caused by *Trichinella spiralis* in man were described. The interstitial lesions in this case were not preserved on account of postmortem changes. The object of this work has been to study the intestinal lesions caused by the *Trichinella spiralis* and the mode of entrance of the embryos. As human tissue was not available, white rats were used.

Askanazy,[2] working with rabbits, described the following intestinal lesions: metamorphosis of cylinder cells to beaker cells, desquamation of the epithelial cells in rows, superficial necrosis of the points of the villi with hemorrhage, destruction of the glandular structure with invasion by leucocytes, and dilatation of the lymph spaces which are filled with a fine granular material. He asserts that an adult female, after winding herself about a villus, pierces the epithelium and connective tissue and finally penetrates into the central lymph space of the villus. Sometimes a whole adult was seen coiled up within the lymph space. The majority of them were in the mucosa, but rarely one was in a lymph space of the submucosa. He described the embryos as free in the lymph spaces of the villi, submucosa, muscle, and subserous layers; also embryos as free in the connective tissue. The latter he considered were born from adults that had not reached the central lymph space. Therefore, he considered that the majority of the embryos were born in the lymph spaces, but a few were born while the adults were within the connective tissue. It seems that probably he has mistaken a glandular crypt, which contained a parasite, for a lymph space. This was due to the fact that the epithelium was entirely wanting, and that the crypt, on account of the plane of the reaction, was surrounded by connective tissue.

Graham,[3] working with rats, reported different observations. He states that the adults lie in the glandular crypts with the epithelium

*From the Laboratory of the Department of the Theory and Practice of Physic, Harvard University.

1. Frothingham: Jour. Med. Research, 1906, xv, 483.
2. Askanazy: Virchow's Arch. f. path. Anat., 1895, cxli, 42.
3. Graham: Arch. f. mikr. Anat., 1897, l, 219.

peeled off, and that they rarely penetrate the connective tissue and then only for a short distance.

Askanazy and Graham, therefore, do not agree on the lesions produced by the parasites or the place of birth of the embryos. That the embryos are in the lymph circulation of the mesenteric glands, and go by this route to the general circulation, is now considered a fact. Stäubli,[4] in a recent article, reviews the literature on this point and adds a few more observations in support of this view. Whether some of the embryos enter directly into the blood stream in the intestines is undecided. In the case which I

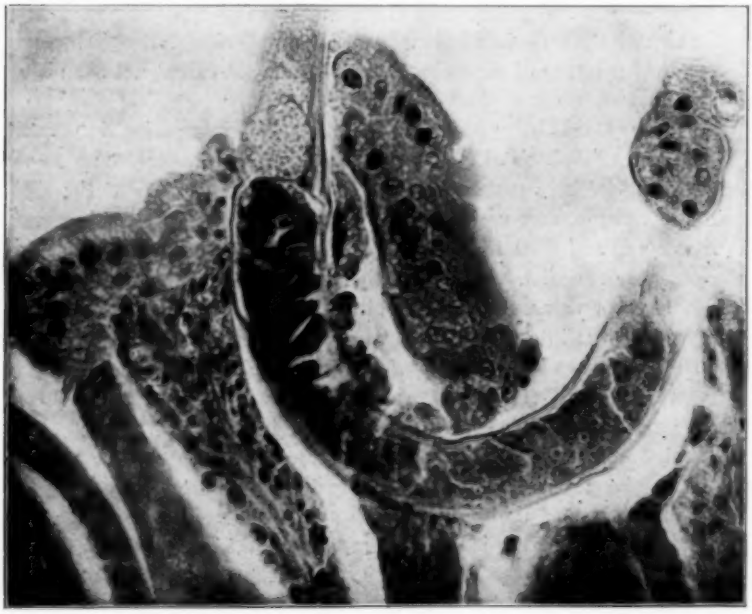

Fig. 1.—Rat 3a: Part of an adult female trichinella which has pierced the epithelium of a villus, worked along between the connective tissue and the epithelium, and emerged again (× 450).

reported[1] an embryo was found free in a liver sinusoid; of course this may have reached there through the general circulation instead of through the portal circulation. It still remains to decide the place of birth of the embryos, their route from their birthplace to the mesenteric glands, and the lesions caused in the intestines by the parasite.

4. Stäubli: Deutsch. Arch. f. klin. Med., 1905-6, lxxxv, 286.

The rats used in this work were fed meat from an infected cat or rat. As postmortem changes occur very soon in the intestines, only those rats were studied whose intestines were fixed in Zenker's fluid immediately after chloroforming. Even then in Rat 1c, which was moribund, degenerative changes were present similar to postmortem degeneration. After Zenker fixation the tissue was mounted in paraffin, cut in serial section and stained with eosin and methylene blue. The following description

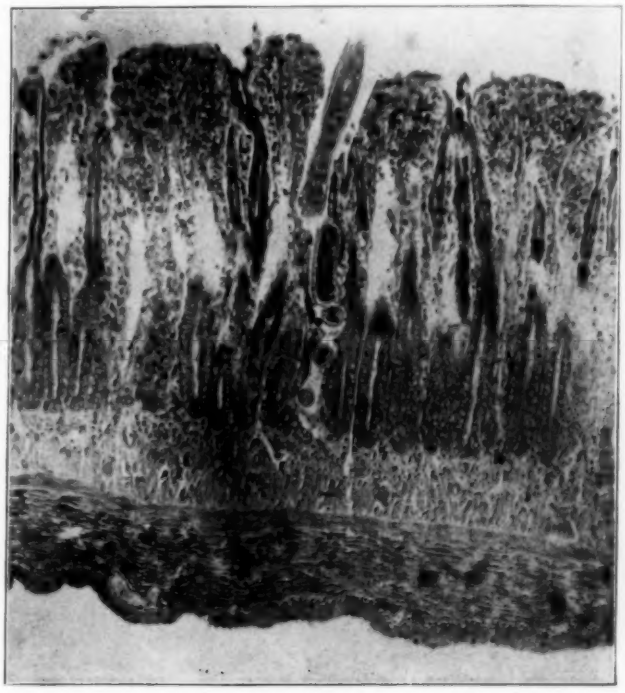

Fig. 2.—Rat 1c: An adult male trichinella which has worked down into a glandular crypt (× 125).

depends on points brought out in the sections of four rats, numbered 3a, 4b, 1c and 4c. Rat 3a was fed infected meat exclusively for twelve days and killed on the thirteenth. Rat 4b was fed infected meat along with other food for twelve days. It survived the infection and was killed four months later. Rat 1c was given one feeding of infected meat on a fasting

stomach and was killed while moribund, three days later. Rat 4c was given one feeding of infected meat on a fasting stomach and was killed nine days later.

The stomach was considerably dilated in Rat 1c and in others that died within a few days of the original feeding. In none of the rats had the parasites entered the gastric mucosa.

In the intestines both male and female parasites, the latter in some cases before impregnation, had entered the mucous membrane, as shown

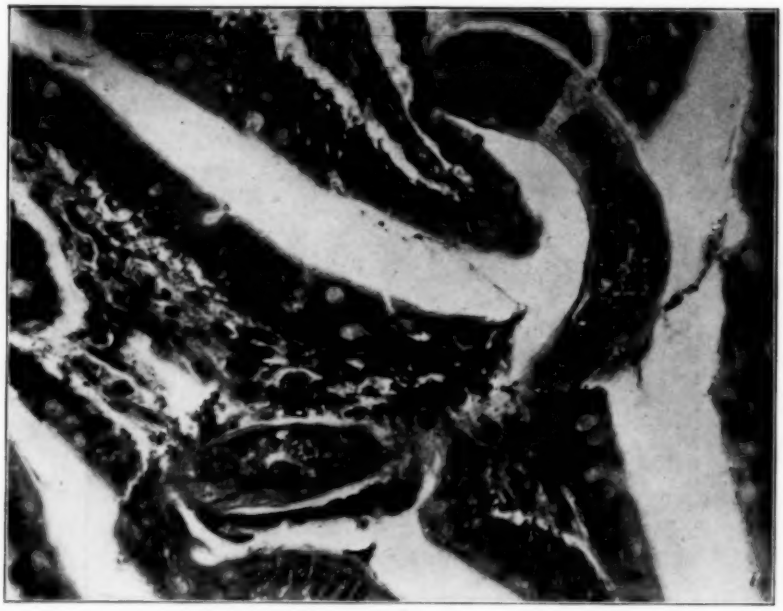

Fig. 3.—Rat 1b: An adult male trichinella piercing the epithelium of several villi (× 450).

by Rat 1c. In the severe infection of Rat 3a the parasites entered the mucosa within a few millimeters of the pylorus, throughout the small intestine and in the first part of the large intestine. By the tenth day both male and female parasites were still present in the mucosa, as shown by Rat 4c. Some of the female parasites at this time contained fully developed embryos, while in others embryos were not fully developed.

Although both Rats 3a and 4c had a systemic infection, neither showed in the intestines any female parasites which had given off all their young. This makes it evident that not all the embryos from one female are born at once, and supports the view now maintained by most writers that the females stay in the intestines for two or three weeks, giving off a few young at a time.

Fig. 4.—Rat 3a: The head of an adult female trichinella working along between the epithelium and connective tissue of a villus. At one point the connective tissue is pushed back but not penetrated (× 900).

The adult parasites, whether young or old, penetrated the mucosa in the same manner. At any point, either at the top of a villus (Figs. 1 and 10) or at the bottom of a glandular crypt (Figs. 2 and 10) they pierced

the epithelium, either perpendicularly or obliquely. This latter point was shown by a section of a parasite entirely surrounded by pressed-back epithelium (Fig. 10). The parasites then worked along between the epithelium and connective tissue. In places they emerged (Figs. 1 and 10) and then some entered again in another place. Frequently the same adult was seen penetrating the epithelium of several villi at once (Figs. 3 and 10). Although the head or body of the parasite pushed back the connective tissue in places, there was no evidence in any of the sections

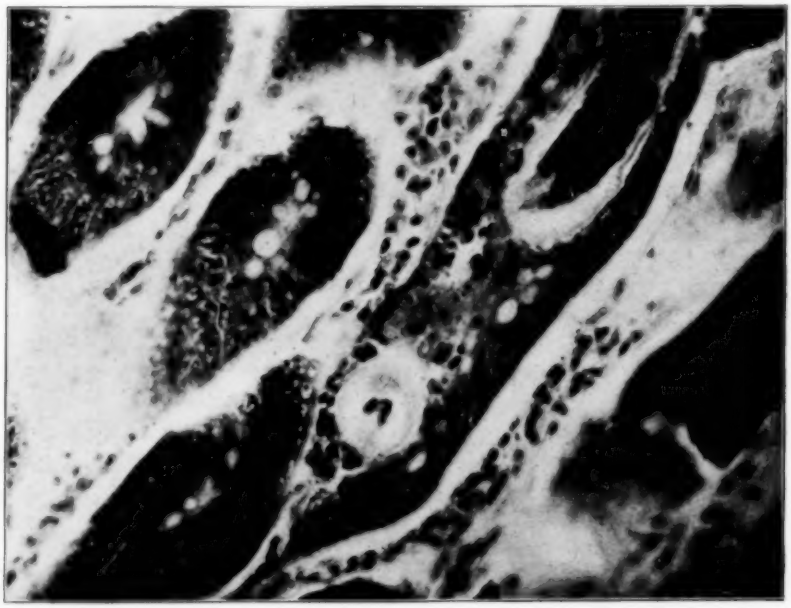

Fig. 5.—Rat 3a: Glandular crypt showing parasite cut in two places by the plane of the section. Crypt contains necrotic epithelium (× 450).

that the adults had penetrated the connective tissue (Figs. 4 and 10). Frequently the body of an adult was seen against the connective tissue at the bottom of a glandular crypt and the head working along under the epithelium toward the lumen of the intestine (Fig. 10). This suggested that the parasite, having worked down the glandular crypt to the connective tissue, could go no farther and so had to turn back to continue its burrowing.

In the glandular crypts where the parasites were the epithelium was desquamated, sometimes entire, sometimes in part (Fig. 10). The desquamated epithelium was necrotic (Fig. 5). In some of the crypts which contained a parasite the only remnant of epithelium was a finely granular basic staining material. In some places this picture of desquamated and necrotic epithelium occurred in glandular crypts where no parasites were present. This suggested that the parasites had been there and gone. The villi in places were quite congested and in a few the blood had broken out

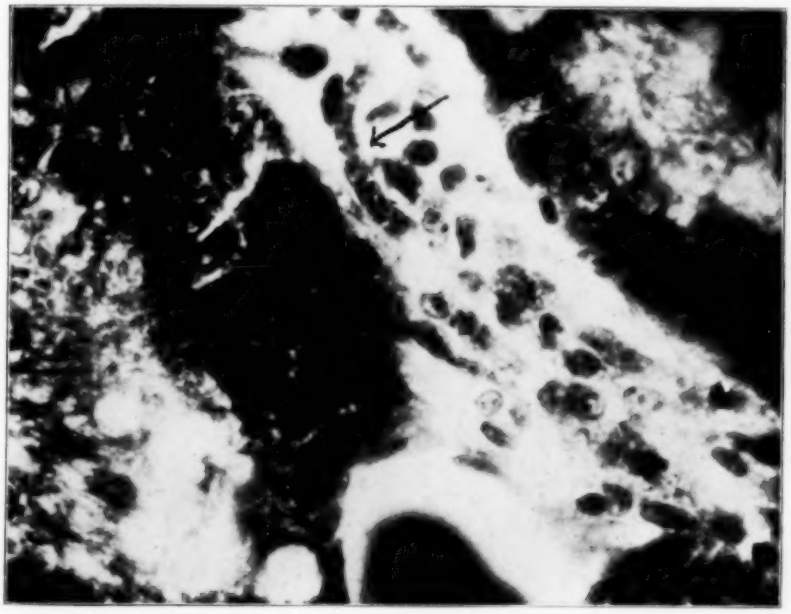

Fig. 6.—Rat 4c: Embryo in part between the connective tissue and epithelium of a villus, in part within connective tissue. Arrow points to embyro. Dark blur at edge an adult female parasite (× 900).

of the vessels. There was no marked cellular reaction upon the part of any of the intestinal layers. Eosinophiles were numerous, but they are so ordinarily in the rat. In Rat 4b all traces of the intestinal lesions had disappeared except for an apparent increase in eosinophilic cells throughout the submucosa.

In Rats 4c and 3a embryos were found in the mesenteric glands, showing that in these cases the usual route to the circulation was taken. Now, since the adult females did not pierce the connective tissue, the embryos must have been born between the epithelium and connective tissue, in the intestinal lumen, or glandular crypts. From there the embryos must have worked actively into the lymph circulation of the mucosa. That the embryos possessed this power of active invasion was shown in striated muscle where they actively penetrated the muscle fibers. Rat 4c showed an embryo with part of its body in the connective tissue of a villus and

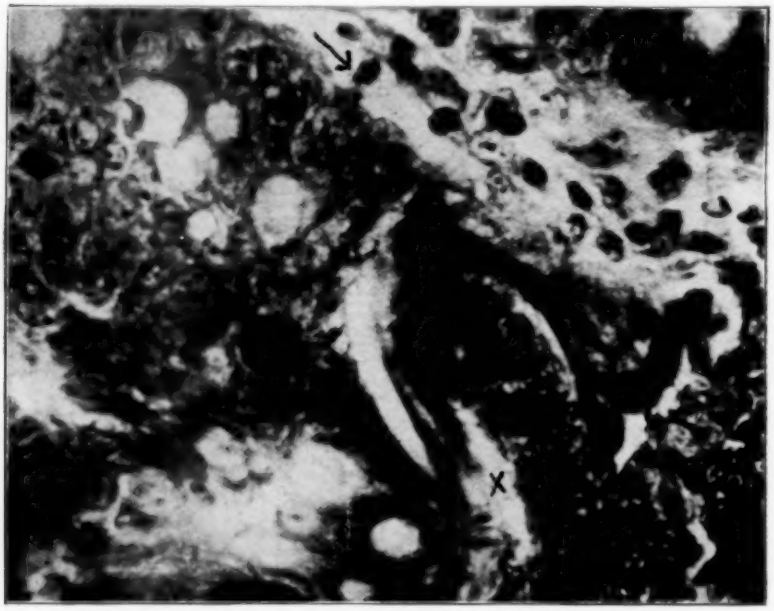

Fig. 7.—Rat 4c: The next section in series to section shown in Figure 6. This shows the same adult female with a space in the vagina. An x marks this space. The epithelium is somewhat elevated from the connective tissue. The black mark to which the arrow points is a cross-section of the same embryo that is seen in Figure 6. It is lying in the space between the epithelium and connective tissue (× 900).

part in the space between the epithelium and connective tissue (Figs. 6 and 7), the epithelium having been separated somewhat from the connective tissue by an adult female (Fig. 7). Since there was no reaction about this embryo it was assumed that it was penetrating the connective

tissue and that it had not been brought there by the circulation and broken out. Furthermore, the same adult female that was elevating the epithelium from the connective tissue contained fully developed embryos in its genital tract except near the vaginal opening (Fig. 7). Usually the embryos crowded the genital tract up to the vaginal opening. This suggested that the embryo in question had just been born from this adult.

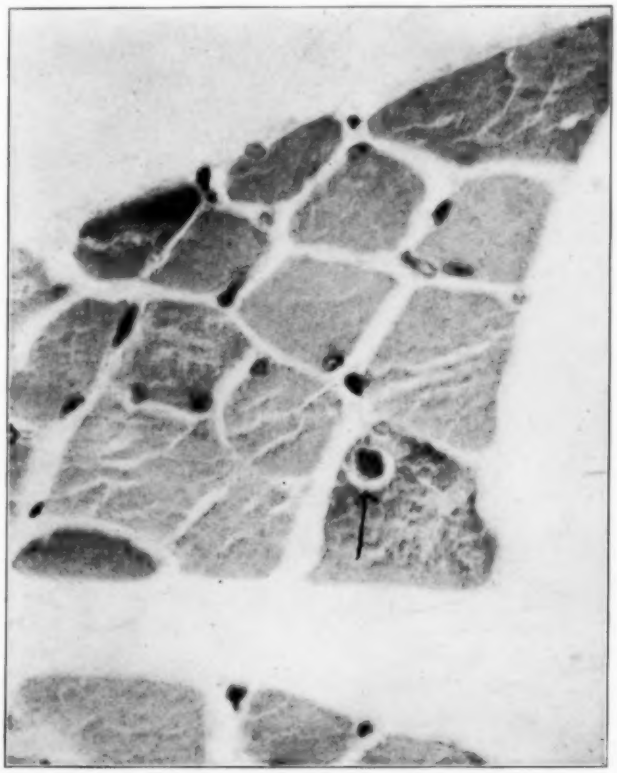

Fig. 8.—Rat 4c: Striated muscle showing practically no reaction. One fiber contains an embryo. Arrow points to embryo (× 900).

In some of the other rats which died embryos were found free in the connective tissue of the mucosa without reaction, surrounding them and apparently not in vessels. This suggested that they were actively invading the connective tissue of the mucosa. The finer details of the structure in these cases, however, were not preserved well enough to make it possible

to state just what their relations were. Also one embryo was seen at the junction of the mucosa and submucosa, but this one was surrounded by a cellular reaction.

One would have expected to find the embryos in the lymph spaces of the submucosa, but, although many sections were examined with this point in view, no embryos were found. This must be accounted for by

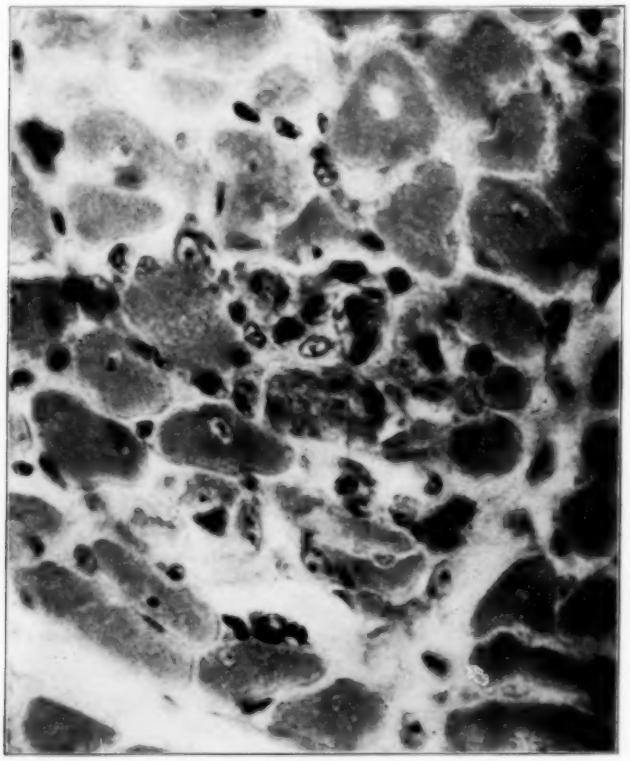

Fig. 9.—Rat 4c: Cardiac muscle showing necrotic muscle fibers invaded by phagocytic cells with a surrounding cellular reaction. An embryo was found in this area, but does not show in the picture (× 900).

the fact that the field of entrance covers such a large space that only a few are born at a time and that the embryos travel quickly when once in the circulation. Where these lymph streams converge, namely, the mesenteric glands, the embryos were found.

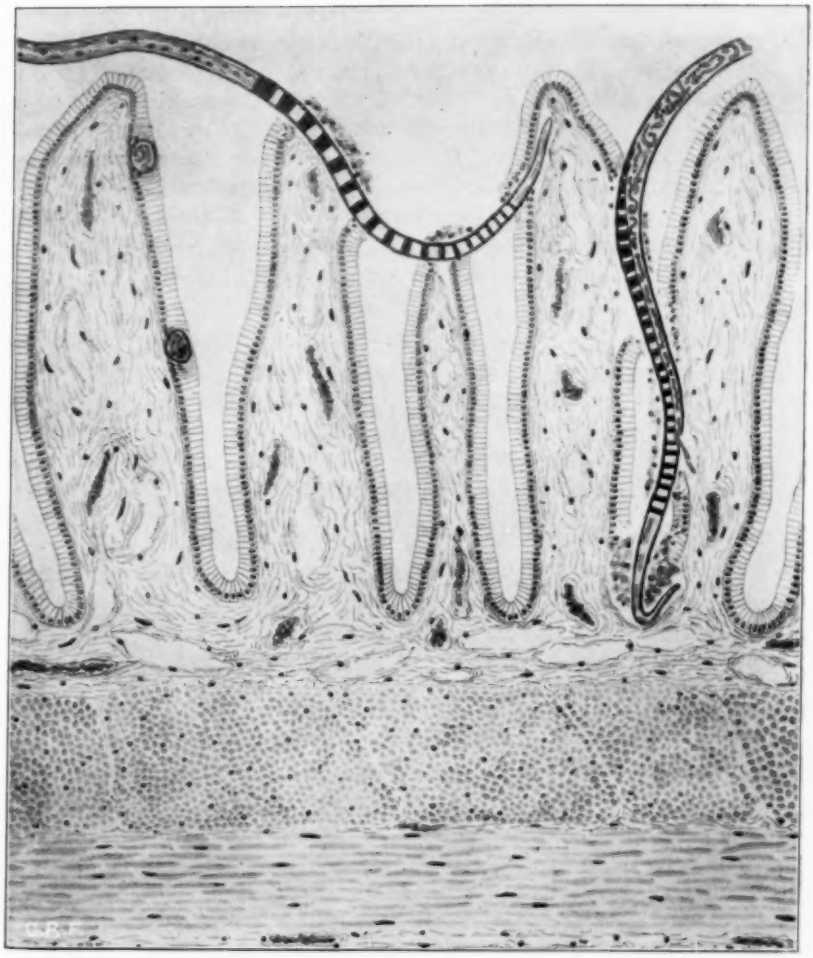

Fig. 10.—Schematic drawing (by C. R. F.) to show method of invasion more clearly. The villus on left shows the cross-section of two parasites piercing the epithelium obliquely. The male parasite touching the three middle villi shows how one parasite may pass to several villi, how it never goes into the connective tissue, and how the peeled-off epithelium becomes necrotic. In the right-hand glandular crypt is an adult female trichinella which has penetrated to the bottom of the gland and then started out again. The epithelium where peeled off is necrotic. An embryo is shown as being born between the epithelium and connective tissue. Here again the adult parasite does not penetrate into the connective tissue.

These rats also showed an interesting fact in regard to the difference in reaction between cardiac and striated muscle. In Rat 4c the embryos were penetrating and within the muscle fibers (Fig. 8). These fibers still retained their striations and in only a few were the nuclei slightly increased. In the same rat the cardiac muscle showed (Fig. 9) many areas of cellular reaction with necrotic muscle fibers which were invaded by phagocytic cells. In several of these areas the embryos could be detected. In Rat 4b, which was killed four months later, no sign of these former processes in the cardiac muscle were present, not even to the extent of a few areas of cellular infiltration or connective tissue increase.

CONCLUSIONS.

Both male and female trichinella parasites penetrate the mucous membrane of the small and large intestine, though chiefly the former. Neither male nor female adult worms penetrate into the connective tissue of the villi or submucosa. The embryos are born a few at a time and actively penetrate through the connective tissue of the mucosa into the lymph spaces. The epithelium where stripped off becomes necrotic. The reaction on the part of the intestinal walls is slight and recovery is complete.

The cardiac muscle fibers are much more sensitive to the presence of the embryos than the striated muscle fibers.

In conclusion I wish to thank Drs. H. A. Christian and F. B. Mallory for their interest and assistance in this work. To Mr. L. S. Brown I am indebted for the microphotographs.

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THE USE OF CERIUM OXALATE FOR THE RELIEF OF VOMITING:

AN EXPERIMENTAL STUDY OF THE EFFECTS OF SOME SALTS OF CERIUM, LANTHANUM, PRASEODYMIUM, NEODYMIUM AND THORIUM.*

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I. INTRODUCTION.

The widely prevalent therapeutic use of cerium oxalate, the many years that it has held a conspicuous position in our pharmacopeia, and the disagreement among medical practitioners as to its therapeutic usefulness, seem to justify the series of investigations that provide the subject of this paper. Diversity of opinion regarding the therapeutic value of cerium oxalate has existed ever since the first introduction of the drug in 1854 by Simpson[1] before the Medico-Chirurgical Society of Edinburgh, and yet a review of the literature has failed to reveal any efforts to solve this mooted question by experimental methods.

Following the lead of Simpson, Lee,[2] Jones[3] and Sommer,[4] many subsequent observers recorded their endorsement of the use of cerium oxalate for the relief of all sorts of gastrointestinal disturbances. Nevertheless, many others have been absolutely unable to achieve any alleviation of the identical disorders by the exhibition of this substance. Were we able to explain all this by the fact that the different cerium oxalate preparations on the market are not of the same composition and, therefore, not of equal value, as has been attempted by a specially appointed committee of the New York County Medical Society,[5] further discussion of this problem might be useless.

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*A preliminary report of this work was made at a meeting of the biologic section of the American Chemical Society in joint session with Section C (Chemistry) of the American Association for the Advancement of Science, New York, December, 1906; Science, 1907, xxv, 455. See also Dreyfuss and Wolf: Am. Jour. Physiol., 1906, xvi, 314; Sollmann and Brown, ibid, 1907, xviii, 426; Chace and Gies, ibid, 1907, xviii, 457. Cossa has detected traces of cerium, lanthanum and didymium (neodymium and praseodymium) in bones (Drechsel in Hermann's Handbuch der Physiologie, 1883, V (i), 609).

1. Simpson: Month. Jour. Med. Sc., 1854, 564; Med. Times and Gaz., 1859.
2. Lee: Am. Jour. Med. Sc., 1860, new series, xl, 391-4.
3. Jones: Chicago Med. Jour., 1861, new series, iv, 65-9.
4. Sommer: Allg. med. Centr.-Ztg., 1883, lii, 353.
5. Rep. N. Y. County Med. Soc., Drug. Circ. and Chem. Gaz., 1880, xxiv, 166.

Although the proportions of the oxalate of cerium and of the related substances usually associated with it in the commercial cerium oxalate vary considerably, and with them the chemical, physical and pharmacologic properties of the product, the comparative insolubility of the cerium oxalate as well as the associated oxalates of other "rare earths," suggests that their action individually and collectively in the usual dose is simply local.

Shortly after the introduction of the drug by Simpson, Mills[6] attempted to explain the influence of cerium oxalate by assuming that it was absorbed from the intestinal tract and acted on the central nervous system. This was the basis for the use of cerium oxalate for cough,[7, 8] at the time Mills wrote (1875), and for its use in the reflex vomiting of early pregnancy at the present time. Ignorance of the fact that cerium oxalate is practically insoluble in most biologic liquids and that it can not be absorbed in significant quantity from the gastrointestinal tract, accounts for the opinion, held to-day by many physicians who use the drug, that its therapeutic action is the result of its being a nervous sedative.

Nowhere has any one recorded observations of any value regarding the toxicity of cerium oxalate. Even the present-day text-books, in the meager paragraph usually devoted to it, record the simple statement that somewhere some one has observed a slight dryness of the mouth after administration of large doses. Obviously this is a rather vague symptom and one concerning which a clinical observer might easily be mistaken. No writer on the subject seems ever to have committed himself to the statement that he himself observed this symptom. Every one who has mentioned it has merely quoted Clark.[8]

Our first object, in the following series of experiments, was to ascertain whether in excessive doses cerium oxalate might cause toxic symptoms.

2. *EXPERIMENTAL.*

A. THE TOXICITY OF CERIUM OXALATE AND THE OXALATES OF LANTHANUM, NEODYMIUM, PRASEODYMIUM AND THORIUM.

In view of the fact that commercial cerium oxalate is really a mixture of the oxalate of cerium with the oxalates of lanthanum, neodymium, praseodymium and thorium, experiments were carried out not only with the commercial product, but also with representatives of each of its leading constituents.

6. Mills: Philadelphia Med. Times, 1875, vi, 148-171.
7. Cheesman: Pharm. Era, 1876, ii, 302.
8. Clark, quoted by F. E. Image: Drug Circ. and Chem. Gaz., 1878, xxii, 170.

The dogs used in this series weighed between 10 and 15 kilograms and each day were fed a meal consisting of 15 gm. meat, 4 gm. cracker meal, 3 gm. lard, 1 gm. bone ash and 35 c.c. water per kilo of weight. On this diet the dogs were kept in approximate nitrogenous equilibrium. Four dogs were used for this series of experiments—one for each of Experiments 1, 5 and 6, and a fourth for Experiments 2, 3 and 4. The oxalate was administered by mixing it with the food. Even the large doses failed to disturb the appetites of the dogs. In each case the animals were kept in a cage,[9] so that careful observations could be maintained on their general condition as well as on their weight, the volume, specific gravity, reaction, etc., of their urine, and the weight and condition of their feces.

EXPERIMENT 1.—*With Commercial Cerium Oxalate.*—Beginning with 0.01 gm., the dose was steadily increased daily for twelve days. On the second day 0.1 gm. was given; then 0.15, 0.3. 0.6, 1, 2, 4, 8, 12, 25, and on the twelfth day 50 gm. These quantities were each administered in a single dose. Yet even when the 50 gm. were given, absolutely no symptoms were elicited beyond an increase in the amount of feces evacuated daily, a symptom following the administration of any inert powder in such large quantities.

A few days after the discontinuance of this experiment the dog successfully delivered herself of a litter of five robust pups. This is of not a little interest clinically, for in its therapeutic use cerium oxalate is more often administered during pregnancy than under any other condition.

EXPERIMENT 2.—*With Chemically Pure Cerium Oxalate.*—Chemically pure cerium oxalate was administered for three successive days in single doses of 25, 40, and 50 gm. respectively. Here again no untoward manifestations were observed. But whereas the quantity of feces this dog normally evacuated varied only between 23 and 37 gm. per diem, on the day that the last dose was given he passed 71 gm. and on the following day 91 gm. On the second and third day following the discontinuance of the salt the fecal weight fell to 21.5 gm. and 10 gm. respectively.

EXPERIMENTS 3 AND 4.—*With Neodymium Oxalate and Thorium Oxalate.*—After a two days' interval, the animal used in Experiment 2 was dosed with neodymium oxalate for three days, 6, 10 and 18.5 gm. respectively; and, during the three days following this, a total of 44 gm. of thorium oxalate was given. The increased elimination of feces was again evident, though not to so marked an extent, the maximum, 56 gm., being reached on the day following the last dose. There were no symptoms.

EXPERIMENT 5.—*With Praseodymium Oxalate.*—Here another animal was given 7, 11 and 14 gm. of praseodymium oxalate on three successive days. The maximum amount of feces, 98 gm., was obtained on the day following the last dose, as before. The only thing remarked was that on this day portions of the feces were softer than usual.

EXPERIMENT 6.—*With Lanthanum Oxalate.*—The fourth dog received three doses of lanthanum oxalate in three days, 10.6, 18 and 22.5 gm. respectively.

9. Gies: Am. Jour. Physiol., 1905, xiv, 403.

Nothing exceptional was noted, though, as in all the previous experiments, observations of the dog were continued for at least a week.

Conclusions.—Only one conclusion can be deduced from this series of experiments. Cerium oxalate and the other oxalates named above are practically harmless, at least for dogs. How much *good* may be done by cerium oxalate was our purpose to determine in the series of experiments described below (B).

Most observers who have used the drug empirically concluded from its insolubility that it acted simply as a local protective to the gastrointestinal tract. We have determined that, though in the ordinary doses a few milligrams of the cerium oxalate would commonly go into solution in the dilute acid of the gastric juice, the dissolved portion would be promptly precipitated (as carbonate, phosphate, etc.) in the intestine, under the influence of the alkaline intestinal juices. This fact, together with the above demonstration of the harmlessness of the drug, would tend to substantiate the mechanical theory of its action. Any other theory is certainly rendered improbable when we consider that the administration of 50 gm. of cerium oxalate gives no evident manifestations of absorption of the compound.

B. DETERMINATION OF THE EFFECT OF COMMERCIAL CERIUM OXALATE ON VOMITING INDUCED WITH APOMORPHIN HYDROCHLORID AND IPECAC.

With the exception of a few other indications, cerium oxalate is at present used almost exclusively for the relief of vomiting, and more particularly for the relief of the early vomiting of pregnancy. As this is supposed to be reflex in origin, we attempted to simulate it in dogs by giving an emetic which acted on the vomiting center. The mechanism of this latter process certainly is not entirely analogous to that of the early vomiting of pregnancy, but it does coincide with it in so much as both are vomiting of central origin.

For this purpose apomorphin hydrochlorid was chosen because of the convenience of its administration and the ease with which its minimum emetic dose can be determined. This for a dog was found to be about 2 to 3 mg.

SERIES 1: VOMITING INDUCED WITH APOMORPHIN HYDROCHLORID.

EXPERIMENT 7.—A dog weighing 14 kilos was used. After three trials it was found that a hypodermic injection of 2.5 mg. of the apomorphin would induce vomiting in ten or fifteen minutes when given on an empty stomach. The animal was not fed for twenty-four hours. Then three doses of cerium oxalate of 3 gm. each were given at intervals of thirty minutes. The drug was administered in gelatin capsules. Fifteen minutes after the last dose had been given, 2.5 mg. of apomorphin were injected subcutaneously. In twelve minutes the animal vomited. Apparently the vomiting had not been delayed.

EXPERIMENT 8.—For this experiment a small dog, in which a gastric fistula had been made, was used. It was desired, by administering the drugs through the fistula, to secure a more intimate application of the cerium oxalate to the stomach wall. In this way retention on the inner surface of the esophagus was prevented. Two grams of cerium oxalate were given with the food on each of two successive days. On the third day 2 gm. of cerium oxalate were introduced by way of the fistula and an hour later 2 mg. of apomorphin were injected hypodermically. In fifteen minutes vomiting ensued.

EXPERIMENT 9.—A dog weighing 24 kilos was given 0.7 gm. of cerium oxalate with food. This was followed, in fifteen minutes, by 3.5 mg. of apomorphin. The animal vomited in nine minutes. As in experiments 7 and 8, the vomiting was not only not prevented, but not even delayed.

In the second series of experiments it was desired to induce vomiting by local irritation of the gastric mucosa, and ipecac was chosen as the most efficient drug. After extensive experimentation it has been definitely proved that emesis following the taking of ipecac is wholly due to local action on the gastric mucous membrane. Those who deny this have never given the subject more than a superficial consideration. Cushny,[10] after carefully considering the experimental evidence on this question, states that "almost all the facts point to peripheral gastric and not central action"; also that "almost all the evidence of this supposed central action has been disproved."

SERIES 2: VOMITING INDUCED WITH IPECAC.

EXPERIMENT 10.—To a new control dog, 4 c.c. of syrup of ipecac were given in milk. He vomited in twenty minutes and again in ten minutes. Each time after vomiting, he defecated. An hour later 1.5 gm. of cerium oxalate were administered in milk and forty-five minutes later 4 c.c. of syrup of ipecac. Ten minutes later, to anticipate vomiting, 1.5 gm. of cerium oxalate were again administered. Nevertheless the dog vomited twenty minutes after the ipecac had been administered.

EXPERIMENT 11.—The gastric fistula dog which was used in experiment 8 was utilized again for this experiment. On September 14, 1.5 gm. of cerium oxalate were given by fistula; fifteen minutes later, 4 c.c. of ipecac by fistula; ten minutes later, 1.5 gm. of cerium oxalate similarly. The dog vomited fifteen minutes after the administration of the last dose of cerium oxalate. During the next two days cerium oxalate was administered daily in order to get the dog more thoroughly under the influence of cerium if possible.

September 15: 1.5 gm. of cerium oxalate were given in the food.

September 16: 1.5 gm. of cerium oxalate were given in the food.

September 17: 2 gm. of cerium oxalate were put into the stomach through the fistula and immediately followed by 4 c.c. of ipecac. The dog did not vomit. At the end of an hour 2 c.c. of ipecac were placed in the stomach through the fistula. Vomiting occurred in twenty minutes.

September 18: 2 gm. of cerium oxalate, followed in a few minutes by 4 c.c. of ipecac, were given as on the 17th. The dog did not vomit for an hour and fifteen minutes.

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10. Cushny: Pharmacology and Therapeutics, ed. 4, 340-1.

September 19: 2.5 gm. of cerium oxalate were passed through the fistula and several minutes later 5 c.c. of ipecac followed. Vomiting occurred in an hour and thirty minutes. Four hours later 4 c.c. of ipecac were administered by fistula. The dog vomited in an hour.

September 20: 4 c.c. of ipecac were introduced into the stomach through the fistula. Cerium oxalate was not administered. Vomiting occurred in twenty minutes. These results suggested that possibly the action of the ipecac was delayed when cerium oxalate was given over a period of time preceding the administration of ipecac.

A few days later it was noticed that there were some drippings from the fistula wound. In the fear that the fistula might be leaking, the experiment was temporarily discontinued in order to permit the wound to heal up tightly about the canula. No cerium oxalate or other drug was given meanwhile. On October 8 the experiment was continued.

October 8: Again, as a control on the efficiency of the ipecac, we gave no cerium oxalate, but only 4 c.c. of ipecac by fistula. Vomiting occurred in thirty minutes. Later in the day 2 gm. of cerium oxalate were given in food.

October 9: 2 gm. of cerium oxalate were given in food. Six hours later, 2.5 gm. of oxalate were administered through the fistula, followed, in a few minutes, by 4 c.c. of ipecac. Vomiting occurred in an hour and a half, an hour later than in the controls.

October 10: 2 gm. of cerium oxalate were given in food.

October 11: 2.5 gm. of cerium oxalate were administered through the fistula, followed, a few minutes later, by 6 c.c. of ipecac the same way. In fifteen minutes salivation was noticeable but vomiting did not occur.

EXPERIMENT 12.—Small dog, weight 8 kilos; fasted twenty-four hours. Cerium oxalate was administered in gelatin capsules as follows: 10:30 a. m., 2 gm.; 11:45 a. m., 2 gm.; 1 p. m., 2 gm.; 2:45 p. m., 4 gm. At 3 p. m., 4 c.c. syrup of ipecac was given. Two hours passed before vomiting occurred. On the next day, as a control, no cerium oxalate, but only 4 c.c. ipecac were given. Vomiting occurred in thirty minutes.

Conclusions.—The results of the experiments in Series 1 uniformly suggest that cerium oxalate has no influence on vomiting of *central* origin. Many more observations will be necessary before it can be positively affirmed that cerium oxalate has no such influence. But tending to substantiate the theory of the mechanical local action of the drug are the following four points that have been definitely established:

1. The absolute accordance of the results obtained in the experiments of Series 1.

2. The insolubility of the cerium oxalate.

3. The absolute lack of symptoms when cerium oxalate was administered in doses of as much as 50 gm.

4. The inability of many men to obtain with cerium oxalate any alleviation of the reflex vomiting of pregnancy.

In reference to this last point it might be argued that, in attempting to explain the poor results some men have obtained with the drug for this condition, we have simply plunged from Scylla into Charybdis by our inability to explain the good results which other clinicians have ex-

perienced. But in view of the first three points, which indicate that the cerium oxalate is not absorbed from the alimentary tract in appreciable proportions, it seems certainly more rational to assume that, whenever good results have been obtained in the reflex vomiting of early pregnancy, they were hallucinatory, the vomiting ceasing of its own accord or from other causes. One reason probably why so many obstetricians have adhered so long to the use of cerium oxalate and are only too willing to delude themselves with the idea that it is doing good, is that for this condition they have no other drug which is so absolutely harmless as the oxalate of cerium.

As might have been anticipated in a salt resembling bismuth subnitrate in so many particulars, the experiments of Series 2, with the exception of Experiment 10 and the work on the very first day of Experiment 11, indicate that cerium oxalate does have an inhibitory effect on vomiting due to local irritation of the gastric mucous membrane. The data of Experiment 10 and the results of the work on the first day of Experiment 11 do not agree with this, but only for the reason that in these instances sufficient time was not given for the cerium oxalate thoroughly to coat the gastric membrane before the stomach was subjected to the action of the ipecac. During the remainder of Experiment 11 and in Experiment 12, however, sufficient time was given for the attainment of that result, and consequently, as the repeated trials uniformly show, the vomiting was either inhibited entirely or delayed considerably.

C. DETERMINATION OF THE EFFECTS OF CERIUM NITRATE ON VOMITING INDUCED WITH APOMORPHIN HYDROCHLORID.

Since cerium oxalate is still being used for the relief of *reflex* vomiting of early pregnancy and was once recommended for the relief of cough,[7, 8] processes which could only be modified by the absorption of the drug from the alimentary canal and its subsequent action on the central nervous system, we proceeded next to investigate the influence on the organism of cerium in the form of a soluble and absorbable salt.

Cerium nitrate was the soluble salt chosen for this purpose, chiefly because it had formerly been recommended by Simpson[1] for the relief of vomiting. This portion of our work may be considered under two heads: 1, observations of the effects of cerium nitrate on vomiting of central origin, when given by mouth and when given hypodermically, and, 2, observations of the effects of cerium nitrate on the organism in general with a determination of the paths of its excretion from the body

when introduced by mouth, hypodermically, intraperitoneally or intravenously.

As a preliminary procedure, an attempt was made to ascertain the most advantageous dose of cerium nitrate to be given by mouth. The details are too numerous and not sufficiently instructive to warrant their interpolation at this point. But after repeated experimentation on five dogs of ordinary size it was determined that on any dose beyond 4 gm., if given with meat (15 gm. per kilo of body weight) and 0.5 gm. if given alone in a gelatin capsule, nausea, vomiting and violent retching and diarrhea, with tenesmus, ensued. Smaller doses elicited no observable symptom. The difference between the permissible quantities in the two methods of administration is easily explained by the fact that cerium combines readily with the proteins of meat.

In Experiments 13 and 14 each dose of cerium nitrate was given in a large gelatin capsule and the dog forcibly made to swallow this. No food was given with it.

In the remaining four experiments of this group (15-18), the cerium was injected hypodermically. Difficulty was experienced in attempting to introduce the drug in this manner owing to the great avidity with which the salt combined with the protein of the tissues. In every case there developed a localized area of necrosis at the site of the injection, and within a week or two this would ulcerate through the animal's hide. Before this could take place the experiments were always completed.

EXPERIMENT 13.—One-half gram of cerium nitrate was given in a gelatin capsule to one of the dogs to which it had previously been administered in connection with the preliminary determination of the limits of advantageous dosage. After forty-five minutes 2.5 mg. of apomorphin hydrochlorid were injected hypodermically. The dog vomited twice within five minutes.

EXPERIMENT 14.—Cerium nitrate was given by mouth in gelatin capsule as follows: 10 a. m., 0.2 gm.; 10:15, 0.1 gm.; 10:30, 0.1 gm.; 10.45, 0.1 gm; 12:00, 0.1 gm. At 12:15, 2.5 mg. of apomorphin hydochlorid were injected subcutaneously. In fifteen minutes the dog vomited. On the next day, as a control test, the dose of apomorphin was given alone and the dog vomited once in fifteen minutes and again five minutes later.

EXPERIMENT 15.—The dog was given 0.3 gm. of cerium nitrate in 5 c.c. of physiologic salt solution by hypodermic injection. Five minutes later, 2 mg. of apomorphin were similarly introduced. Vomiting occurred very profusely in eight minutes and continued intermittently for fifteen to twenty minutes. Five days later 2 mg. of apomorphin hydrochlorid followed by 2 gm. of cerium nitrate were injected hypodermically. Vomiting took place in five minutes.

EXPERIMENT 16.—For this experiment we used the gastric fistula dog that had been employed in experiments 8 and 11, but which had not been subjected to experimental treatment for a month and a half previously. Hypodermic injections were made as follows: At 2:55, 1 gm. of cerium nitrate; at 3:14, 1 gm. of cerium nitrate; at 3.15, 2 gm. of apomorphin. At 3:20 the dog defecated soft feces and afterward strained; then licked his chops, showing nausea, but did

not vomit. As a control test, 2 mg. of apomorphin hydrochlorid were injected at 5:40, without accompanying cerium dosage. In seven minutes the dog vomited twice. On the next day, 2 mg. of apomorphin hydrochlorid were injected subcutaneously, followed in five minutes by a hypodermic dose of 2 gm. of cerium nitrate. Vomiting did not occur. As a control test, two hours later 2 mg. of apomorphin hydrochlorid were given alone and the dog vomited three times in fifteen minutes.

EXPERIMENT 17.—For this experiment we used one of the dogs which, like the one employed in Experiment 13, had previously been given cerium nitrate by mouth in connection with the determination of the limits of advantageous dosage. During the first experiment to which this dog had been subjected, he suffered from diarrhea and vomiting for a few days as a result of the cerium nitrate treatment, but during the week which intervened between that experiment and this one, he was perfectly well.

December 6: 2 mg. of apomorphin hydrochlorid were injected subcutaneously, followed immediately by a hypodermic dose of 2 gm. of cerium nitrate. In five minutes the dog vomited profusely, continuing to do so intermittently for ten minutes.

December 7: 2 gm. of cerium nitrate were injected subcutaneously to determine whether this dose may have caused the vomiting observed yesterday. The outcome was entirely negative.

December 10: 2 mg. of apomorphin hydrochlorid were given alone hypodermically as a control test. In five minutes the dog defecated and vomited several times.

December 11: The first part of the experiment was repeated. A dose of 2 gm. of cerium nitrate was followed by one of 1.5 mg. of apomorphin hydrochlorid (note the small quantities used). The dog vomited twice in ten minutes.

EXPERIMENT 18.—A new dog was used for this experiment.

December 13: 2 mg. of apomorphin hydrochlorid were administered subcutaneously. The dog vomited three times in thirteen minutes. This result served as a control observation. Three hours later, 1 gm. of cerium nitrate was injected and three minutes afterward, 2 mg. of apomorphin hydrochlorid. Vomiting did not occur. Two hours later, as a second control, 2 mg. of apomorphin hydrochlorid were injected alone. The dog vomiting three times in eight minutes.

December 14. The entire experiment was repeated as follows: 1 gm. of cerium nitrate was injected. Twenty minutes later another gram of cerium nitrate was injected, immediately followed by 2 mg. of apomorphin hydrochlorid. Vomiting did not occur.

December 15: As a third control, 2 mg. of apomorphin hydrochlorid were injected alone. Vomiting occurred in fifteen minutes.

Conclusions.—Experiments 13 and 14 agree in indicating the absence of any inhibitory effect of cerium nitrate, *administered per os,* on centric vomiting. Experiments 15 and 17 seem similarly to demonstrate the absence of any such inhibitory effect of the cerium nitrate when *injected hypodermically.* On the other hand, Experiments 16 and 18 directly controvert this and seem to show that cerium nitrate administered hypodermically does inhibit vomiting of centric origin. The discordance between these results render an interpretation of them rather difficult. Additional experiments will be necessary for final removal of the uncertainty in this connection.

D. DETERMINATION OF THE GENERAL EFFECTS OF CERIUM NITRATE ON THE BODY AND ALSO OF THE PATHS OF EXCRETION OF CERIUM FROM THE ORGANISM.

In the remaining experiments described in this paper cerium nitrate was introduced into the body in four ways: 1, per os; 2, hypodermically; 3, intraperitoneally, and, 4, intravenously. The method used in each case is indicated in the description of that experiment. In each instance symptoms are also described, if any were induced, and the autopsy findings as well as the results of analysis of urine, feces and the various organs are recorded.

The method used for the detection of cerium was simple and accurate. Our own tests showed that a fraction of a milligram of cerium could be detected by it. If the material to be analyzed was a liquid, such as urine or blood, this was first evaporated to dryness. Otherwise the matter under examination, such as muscle, was immediately incinerated. After preliminary heating with the blast-flame, for further ignition of carbon, the ashes were fused with potassium bisulphate. After cooling, the resultant white flux was dissolved in a small quantity of dilute nitric acid. The solution was then neutralized with powdered potassium carbonate to precipitate iron, and filtered. The clear filtrate was reacidified with nitric acid, heated, treated with a few grams of lead peroxid and the mixture then boiled for a minute or two. When the particles of the oxid of lead settled to the bottom of the beaker, the supernatant fluid showed a canary yellow tint if cerium was present. Most minute traces could be detected in this way.

EXPERIMENT 19.—*Administration per Os with the Food.*—December 14, 6 gm.; December 15, 8 gm.; December 16, 17 and 18, 9 gm. daily; December 19 to 29, inclusive, 10 gm. each day. No symptoms. On the 29th the animal was killed with chloroform. Autopsy showed that all organs were normal. The daily urines were free from cerium. The daily feces from the 15th to the 28th, contained cerium. The liver contained a small quantity of cerium, but none was found in bile from the gall bladder nor in the spleen.

EXPERIMENT 20.—*Hypodermic Administration.*—On December 13, two doses of 1 gm. each were given with an interval of twenty minutes between doses. On December 14, 1 gm. was given twice with an interval of twenty minutes between doses. The dog gradually lost his appetite. In a day or two he refused all food and his anorexia continued to the end of the experiment. On his back two fluctuating areas appeared which apparently were liquefied necrotic tissue produced by the corrosive action of the injected cerium nitrate. His stools became more and more diarrheal in character until, by December 22, he several times defecated material resembling diluted red blood. When offered some water he eagerly drank all of it, but five minutes later he vomited it all. Later in the day he was killed by chloroform. The autopsy immediately afterward revealed the following facts:

Autopsy.—When the abdomen was opened, attention was at once attracted by the unusual violence of the gastric and intestinal peristalsis. On examination, the intestine was found to be empty except in the lower part of the ileum, where there were numbers of yellowish white intestinal worms, such as frequently occur in dogs that otherwise appear to be normal. The entire intestinal tract showed marked congestion of its mucosa, more especially observable in the lower part of the ileum and throughout the large gut. In these situations, also, numerous petechial spots and large areas of ecchymosis were present, in the large intestine occupying the greater part of its surface. The other organs were seemingly normal.

EXPERIMENT 21.—*Hypodermic Administration.*—Weight of dog, 10 kilos. The site of injection was thoroughly washed so as to prevent the dog from licking it, and so possibly getting a little cerium in his mouth. On February 18, 19 and 20, 0.1 gm. was given daily; February 21, 0.1 gm. at 8 a. m. and 0.2 gm. at 2 p. m.; February 22 and 23, 0.2 gm. each day; February 24, 0.5 gm. February 25 the dog was killed with chloroform.

Autopsy and Analyses.—The autopsy showed areas of intense congestion of the intestinal mucous membrane, especially of the small intestines. The daily urines did not contain cerium. The feces eliminated on February 24 and 25 contained cerium. The intestinal walls contained relatively large quantities of cerium. The liver, spleen and blood contained traces. Muscle from the site of the injection gave a strong response to the test for cerium. The results of the examination of the gall bladder containing bile, and of the brain and kidneys were negative.

EXPERIMENT 22.—*Hypodermic Administration.*—As in Experiment 21. Weight of dog, 6 kilos. On March 18 and 19, 0.2 gm. was administered each day; on March 20 and 21, 0.4 gm. each day; on March 22 and 23, 0.6 gm. daily; March 24, 0.8 gm.; March 25, 1.5 gm. On the 21st, dark bloody material began to appear in small quantities in the stools, but there was no diarrhea. The animal was well otherwise, and was killed with chloroform on the 26th.

Autopsy and Analyses.—On autopsy, blood and much mucus were found in the intestinal contents. The mucous membranes of the large and small intestines were congested and both showed areas of ecchymosis. The daily urines and feces were free from cerium. The parts that showed the presence of cerium were the liver, spleen, blood and tissues from the site of injection. The intestines were not analyzed, but the intestinal contents gave a strong test for cerium.

EXPERIMENT 23.—*Hypodermic Administration.*—As in Experiments 21 and 22. Weight of dog, 6.5 kilos. On the first day 0.2 gm. was administered; on the second and third, 0.4 gm.; on the fourth and fifth, 0.6 gm.; on the sixth, 0.8 gm.; on the seventh, 1 gm. There were no intestinal symptoms and no diarrhea. The animal was killed with chloroform on the eighth day. *Autopsy* showed nothing unusual.

Analyses.—The feces eliminated on the sixth, seventh and eighth days contained cerium. The intestines contained cerium, but the liver and spleen did not.

EXPERIMENT 24.—*Intraperitoneal Administration.*—First day: With the dog under slight anesthesia, 1 gm. of cerium nitrate dissolved in 15 c.c. of physiologic salt solution was injected into the peritoneal cavity. Immediately after the operation the dog began to vomit and did so almost continuously for nearly an hour. Vomiting then became gradually less frequent during the next hour, and it occurred only occasionally during the succeeding five hours. Except at the very onset, the vomitus consisted merely of mucus. Besides this sign of peritoneal irritation, the dog exhibited rigidity of his abdominal muscles and tender

ness of his abdomen to pressure, and manifested a desire to remain absolutely quiet.

Second day: On the following day the animal appeared apathetic and only responded sluggishly to call. His abdomen was then no longer tender, but when it was squeezed from side to side a gurgling sound could be elicited. He refused to eat and one time, on attempting to drink, vomited.

Third day: The apathy had entirely disappeared. The dog seemed to be himself again. The anorexia still persisted, but to it diarrhea was now added.

Fourth day: Diarrhea was almost continuous. The dog refused to eat.

Fifth and sixth days: The dog still declined to eat, but now began to drink freely, voided foul-smelling stools, which were fluid, and with them exhibited tenesmus.

Seventh day: The diarrhea continued. The dog ate a small quantity of meat, but a little later vomited relatively large solid chunks covered with tenacious mucus.

Eighth day: During the afternoon of this day, the animal began to stagger around in his cage blindly. With intervals of quiet, he did this several times. The condition of his bowels persisted. At midnight he was still alive, though very sick.

Ninth day: The dog was found dead in the morning.

Autopsy.—The heart was in systole. The lungs were very edematous, full of frothy fluid. The peritoneum had everywhere lost its glistening sheen and scattered throughout it were small white spots, which proved on analysis to be composed almost entirely of cerium. The intestines were matted together into an almost inextricable mass. The omentum especially was shrivelled into a small mass of fat adherent to the parietal peritoneum. The mesentery was also drawn together and showed several small hemorrhages between its layers. Both liver and spleen were very much deformed and their capsules thickened into a parchment-like tissue, which cracked on handling. In the case of the liver this condition on cross-section was also found to extend into the interlobular septa. The gall bladder was contracted and was empty, its walls, together with the retroperitoneal fat, similarly coagulated. Especially along the ureter this condition pertained to such an extent as to give the ureter in spots a calcareous feeling. The bladder was thin-walled and cracked beneath the fingers. No changes were observable in the interior of the kidneys. Soft brownish feces occupied the intestines. The small intestine showed marked congestion of its mucosa, numerous petechiæ and large patches of ecchymosis.

Tests for Cerium.—The mucus vomited on the first day did not contain cerium. It was impossible to analyze normally voided urine because some of the diarrheal stools were always mixed with it. Feces passed during the first three days were free from cerium, but from the fourth day onward they showed the presence of cerium.

Organs: It was impossible to analyze the intestines or the abdominal organs because of cerium protein compound on their peritoneal surface. Muscle, kidney (a section from the center), heart and brain were free from cerium.

EXPERIMENT 25.—*Intravenous Introduction.*—Weight of the dog, 10.5 kilos. Dose, 0.1 gm. of cerium nitrate in 40 c.c. of physiologic salt solution, injected into a femoral vein under ether anesthesia. On coming out of anesthesia the dog shivered violently for almost an hour and was salivated profusely. Fifteen minutes after the injection the dog eliminated feces of normal consistence and color, and eight minutes later again defecated, but the feces were now soft, pasty and chocolate-colored. Four hours later the dog vomited once and passed fluid feces.

Second day: The feces were still slightly diarrheal. Otherwise the dog had entirely recoverd.

Third day: The feces were still a little pasty and dark in color. The dog was killed with chloroform. Autopsy was negative.

Tests for Cerium.—Feces, urine, spleen, heart and intestines negative for cerium.

EXPERIMENT 26.—*Intravenous Introduction.*—Weight of the dog, 15 kilos. Blood had been extracted from this animal in another connection several weeks before the beginning of this experiment. Dose: 0.1 gram of cerium nitrate in 40 c.c. of physiologic salt solution, injected into a femoral vein under ether anesthesia. The operation was completed at 11:30 a. m. After the operation, the dog had no gastrointestinal symptoms whatever, but was salivated profusely. During the night he vomited.

Second day: The animal was very quiet and refused to eat. Stools were diarrheal.

Third day: The dog retched and vomited several times. It was killed with chloroform at 11:30 a. m.

Autopsy.—All the organs were normal except the spleen. This had many blackish hemispherical protuberances on its surface, averaging ⅛ to ¼ inch in diameter. On section they were dark red and jelly-like. Microscopic section demonstrated these to be hematomata, which were just beginning to organize. These hematomata must have been caused by the blood-letting operation to which the dog had been previously subjected, as has already been noted. The spleen itself showed a mild chronic intestinal splenitis, the origin of which we were unable to ascertain.

Tests for Cerium.—Feces: First day, negative; second day, positive for cerium. Saliva: negative. Liver and spleen: positive. Intestines: positive, very strongly.

Conclusions.—Cerium *nitrate,* irrespective of the channel of its introduction into the body, whether by mouth, hypodermically, intraperitoneally or intravenously, generally caused the following effects:

1. Gastrointestinal symptoms (vomiting and diarrhea).

2. Congestion and ecchymoses in the intestinal mucosa, as demonstrated by the autopsies.

3. To these results may be added the further fact that cerium was usually eliminated in the feces, but was never found in the urine.

4. The presence of cerium was usually demonstrated in the intestines (washed free of their contents). As a rule, much greater quantities of cerium were found in the intestines than in any other organ. The liver and spleen usually contained some cerium, but never as much as the intestines did.

The four above-mentioned observations lead directly to the general conclusion that, however introduced into the organism, cerium leaves the body by the alimentary canal and is excreted, in great part at least, through the intestinal wall. From the fact that some cerium was found in the liver, it may be inferred that possibly a small quantity was also

excreted by the liver into the bile, even though none was ever demonstrated therein. Cerium did not leave the body through the kidneys in appreciable quantities.

3. GENERAL SUMMARY.

The conclusions at which we have finally arrived, in addition to those just summarized, are the following:

1. Commercial cerium *oxalate* is non-toxic.

2. Cerium oxalate has no inhibitory effect whatever on vomiting of *central* origin.

3. Cerium oxalate may inhibit vomiting due to *local irritation* of the gastric mucosa, but only if given in large doses for some time so as to coat the stomach wall pretty generally.

4. Cerium oxalate is not absorbed from the gastrointestinal tract.

These four propositions complete a very close analogy between cerium oxalate and bismuth subnitrate. Both salts are insoluble and, because of this property, neither is absorbed from the gastrointestinal tract. This latter fact, in the case of bismuth, has resulted in its use for various local disorders of the alimentary canal, but, so far as the literature furnishes any evidence, the use of cerium oxalate has been directed, in great part against the reflex vomiting of early pregnancy, a condition in which no one could rationally think of using bismuth.

It certainly seems reasonable to suppose that cerium oxalate ought to prove efficacious in alleviating all those conditions for which bismuth is at present used;[11] in other words, those in which a protective coating to the wall of the viscus is desired. In this respect its use is at present extending; for instance, some men find it efficient for relieving the irritability of the stomach in alcoholic gastritis, others for allaying the gastric disturbances that occasionally manifest themselves in the course of infectious diseases.

There is no reason for doubting its value in these and similar conditions, such as gastric ulcer, in which the vomiting is due to a local irritation of the mucous membrane. But in the doses that some men prescribe, 0.15 gm. to 0.20 gm., it can hardly be hoped that it will prove efficient. In view of the manner in which it now appears that cerium

11. Quite pertinent in this relation are the recent reports of cases of nitrite poisoning following the administration of bismuth subnitrate, especially in children, and the animal experimentations of Böhme upon the toxicology of bismuth subnitrate and its decomposition into nitrites by the bacterial flora of the feces. Böhme (A.): Arch. f. exper. Path. u. Pharmakol., 1907, lvii, 441-452. Wilcke: Ztschr. f. Med.-Beamte, 1908, xxi, 268-271. Worden, Sailer, Pancoast and Davis: Univ. of Penn. Med. Bull., 1908, xix, 122-141.

oxalate accomplishes its purpose, namely, mechanically, by coating the wall of the stomach, these doses seem ridiculously small. Cerium oxalate ought to be administered in doses comparable to those in which bismuth subnitrate is given.

This research was proposed to us by Dr. William J. Gies, was carried out under his supervision, and his suggestions throughout the course of this work were of great value. He wishes us to state that his attention was drawn to this subject by his colleague, Prof. Virgil Coblentz, of the New York College of Pharmacy, who very generously supplied nearly all the material with which our tests were made.

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THE RELATIONS EXISTING BETWEEN BILIRUBINEMIA, UROBILINURIA AND UROBILINEMIA.*

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I. THE QUANTITATIVE DETERMINATION OF BILIRUBIN IN BLOOD SERUM.

When one considers the frequency of jaundice as a clinical manifestation and its importance as a diagnostic sign in various diseases, it is somewhat surprising that its detection and measurement should so long have escaped the refinements which come from the application of accurate laboratory methods.

It is the every-day experience that both of the usual means of recognizing the presence of bile pigment in the blood—the visible pigmentation of the skin and mucous membranes and the reaction for bilirubin in the urine—are crude and often unsatisfactory. In the lesser grades of cholemia the urine does not react for bile pigment, and the appearance of the skin and membranes is often such as to leave one wholly in doubt as to whether or not a jaundice really exists.

The examination of the blood itself—the method that would seem to be the most direct and reliable—has failed thus far to come into anything like general use.

A number of tests for bilirubin in blood serum have, however, been devised and used. The simpler of these, such as the methods of Hamel[1] and Posselt,[2] depend on a comparison of the color of the serum to be tested with that of normal serum, and are crude and not entirely trustworthy. Of the several qualitative chemical tests the modification by Syllaba of Gerhardt's procedure is perhaps the best.[3] Until recently no satisfactory quantitative test for bilirubin in the blood was available. In 1903, however, Gilbert and his pupils developed a method of measuring the bilirubin content of blood serum which is simple enough for use in the clinical laboratory and seemed to them to give reasonably accu-

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1. Hamel: Deutsch. med. Wchnschr., 1902, xxviii, 1702.

2. Possett: Zentralbl. f. inn. med., 1907, xxviii, 489.

3. The test recently recommended by Biffi (Folia hæmatologica, 1906, iii, 189) we have not used.

rate results. The method consists in an adaptation of the familiar Gmelin test to fluids rich in albumin, and a standardization of it so that it can be used as a quantitative test.

In such albuminous media the complete Gmelin reaction, that is, the characteristic play of colors, occurs only when bilirubin is present in relatively strong concentrations, for example, between 1 to 3,000 and 1 to 5,000. In strengths of from 1 to 7,000 to 1 to 11,000 the reaction appears as a distinct blue-green ring, but without the color play ("Hayem's reaction"). In weaker solutions of bilirubin the blue ring at the point of contact becomes finer, and has a violet rather than a green reflection, but remains distinct up to a dilution of about 1 to 40,000, beyond which point it ceases to disappear.

Working with well-known strengths of pure bilirubin, Gilbert, Herscher and Posternak[4] have found the limit of this reaction—the point beyond which no distinct blue ring is to be seen—to represent constantly a dilution of approximately 1 to 40,000. Furthermore, they believe that they have proved that this blue ring is characteristic of bilirubin and is not produced by any other substances in the blood, such as albumin, hemoglobin, indican or lutein. It is on this assumption that the limit of the Gmelin reaction in the blood represents a definite strength of bilirubin, that they have based their method of measuring the bilirubin content of blood serum.

Details of the Method of "Cholémimétrie."

The plan consists in making a series of known dilutions of the blood serum to be tested, in tubes of standard size, underlying the fluid in each tube with fuming nitric acid and noting the tube in which only a faint blue ring is visible at the end of a certain period. The bilirubin concentration in this tube is then assumed to be 1 to 40,000, and, the degree of dilution being known, it is easy to calculate the bilirubin concentration in the undiluted blood serum.

APPARATUS REQUIRED.

1. Eight or ten flat-bottomed cylindrical glass tubes 4 or 5 cm. long, with an inside diameter of 1 cm. (It is convenient to have a block of wood or a frame into which these tubes can be set in a row.)

2. Three pipettes: (a) One holding 1.5 c.c. and graduated accurately to 1/20 c.c., for measuring the blood serum; (b), one holding 2 c.c. and graduated to 1/4 c.c., for measuring the diluting fluid ("artificial serum"); (c), one with a tapering point, to measure approximately 1/4 c.c. of the nitric acid reagent.

REAGENTS REQUIRED.

1. The artificial serum: The whites of several eggs are added to an equal volume of 0.7 per cent. sodium chlorid solution; thoroughly mixed, and allowed to stand on ice for twenty-four hours. The liquid is then decanted and to it is

4. Gilbert, Herscher and Posternak: Sur la reaction de Gmelin dans les milieux albumineux, etc., Compt. rend. Soc. d. biol., 1903, lv, 530, 574, 1587.

added caustic soda, in the proportion of 0.5 gm. to 100 c.c. It is then allowed to stand three or four days before using, during which time a precipitate forms which includes the coloring matters of the egg-white. When used the liquid should be perfectly colorless in the thickness of 1 cm. This artificial serum in its fluidity, albumin content and alkalinity approximates blood serum. It should be kept cool, and should be freshly made at least every month.

2. The nitric acid reagent.

Pure HNO_3	200 c.c.
Distilled water	100 c.c.
Sodium nitrite	0.06 gm.

The bottle must be kept carefully stoppered.

TECHNIC.

Distribute in each of, say, 6 glass tubes with the pipette B exactly 0.5 c.c. of artificial serum; then add with pipette A increasing amounts of blood serum (e. g., 1/20 c.c. in the first tube, 2/20 in the second tube, 3/20 in the third, 5/20 in the fourth, 8/20 in the fifth and 12/20 in the sixth tube) and mix by shaking. Underlay the fluid in each tube with 1/4 c.c. of the acid reagent with the pipette C. After standing for thirty minutes the tubes are examined. For this good daylight (not direct sunlight) is needed. The examiner's back should be to the light, the eyes should be somewhat above or below the tubes, rather than on a level with them, and the tubes should be held against a white background. If the blood serum contain sufficient bilirubin, in some of the tubes at the line of contact between the acid and the serum will be seen a clear blue ring, the ring being more pronounced in the tubes containing the larger amounts of blood serum. The tube in which the first faint but distinct blue ring is seen, therefore, is assumed to contain bilirubin in the dilution of 1 to 40,000. (See plate.) The strength of bilirubin in the initial blood serum can then be readily obtained by the following formula.

$$\frac{x = 10 + a}{a}\chi$$

χ represents the fraction 1/40000; a = the number of twentieths of cubic centimeters added.

Example:—If the ring is first seen in the tube to which 5/20 c.c. of blood serum has been added, then:

$$a = 5 \text{ and } x = \frac{10 + 5}{5}\chi = 3/40000 = 1/13333.$$

The blood serum, therefore, contains bilirubin in the ratio of about 1 to 13,300.

If 30/20 c.c. of blood serum are needed to show the ring, then $a = 30$ and the bilirubin content will be 1 to 30,000. If 60/20 c.c. are required the bilirubin content will be 1 to 34,300.

In this case it will be found convenient to use only 30/20 c.c. of the blood serum and add it to 1/4 (instead of 1/2) c.c. of the artificial serum.. The resulting mixture will be the same and a will still equal 60. On the other hand, if bile pigment is present in large amount and the tube containing 1/20 c.c. of blood serum gives too strong a reaction, it will be necessary to mix 1/20 c.c. of blood serum with 1 or even 2 c.c. (instead of 1/2) of artificial serum. Then a = 1/2 or 1/4 and the bilirubin content will be, respectively, 1 to 1900 or 1 to 975.

If undiluted blood serum is needed to give the faint blue ring, the bilirubin content will of course represent a dilution of 1 to 40,000. If bile pigment is present in smaller amounts than this, no blue line can be detected.

In case the blood serum to be tested is of pale color, or is believed to contain only a small amount of bilirubin, instead of beginning the series with 1/20 c.c. of the serum, it is well to begin with a considerably larger quantity and to increase the amount rapidly; for example, in the first tube 16/20 c.c., in the

second 18/20, in the third 20/20, in the fourth 25/20, in the fifth 30/20, in the sixth 40/20. A little experience will enable one to select the dilutions so that the end-reaction shall usually fall somewhere within the series. If it does not, other tubes must be prepared, for it is necessary to have at least one tube in which no blue line can be seen. It is important that the examination be made just half an hour after the tubes have been prepared, as the reaction tends to become stronger on standing and tubes which fail to give a reaction within the specified time may do so after an hour or two.

Using this method, Gilbert and his pupils have established the average bilirubin content of the blood in a large series of normal individuals and in a number of conditions associated with more or less distinct jaundice, such as simply family cholemia, cholelithiasis, pneumonia, chronic interstitial nephritis, advanced heart disease, alcoholic and biliary cirrhosis, icterus gravis, etc.[5] Since the blue ring is found to occur regularly in the undiluted serum of normal persons, Gilbert and Herscher[6] are led to the belief that normal human blood serum contains a minute quantity of bilirubin, such as is known to be present normally in the blood of certain of the lower animals. They found this physiologic cholemia to correspond to a bilirubin strength which varies between 1 to 28,000 and 1 to 40,000, with an average of 1 to 36,500.

Our own experience with this method of measuring the bilirubin content of blood serum covers a period of fifteen months and includes upward of 160 examinations made in about 120 cases. The list of subjects examined includes normal individuals, many patients with pneumonia, nephritis, typhoid fever, heart affections, cancer, tuberculosis, appendicitis, rheumatism and a great variety of affections of the liver and bile passages. In general, our own results, which were constantly controlled by other, qualitative tests, correspond closely with those of Gilbert and his followers.

We have found it advisable, however, to make two slight modifications of the method as above described: first, in making the artificial serum, when sodium hydroxid is added in the strength prescribed (0.5 per cent.) it is frequently impossible to prevent the egg albumin from forming a jelly-like mass. This we have been able to avoid by reducing the strength of the sodium hydroxid to 0.3 per cent. Second, we have found that a much sharper and clearer line of contact between the acid and the serum can be obtained by first putting the acid reagent in the tube and then overlaying this with the mixed serum. This procedure requires the mixing of the artificial and the blood serum before they are

5. See numerous publications in Compt. rend. Soc. d. biol., Paris, during the years 1903, 1904 and 1905.

6. Gilbert and Herscher: Compt. rend. Soc. de biol., 1905, lviii, 899.

placed in the tubes and, therefore, takes a little more time, but it increases materially the distinctness of the reaction.

We have found that one quickly acquires facility in recognizing the end-reaction and have been surprised to see how closely the independent readings of the same tests by different persons agree. The test is open to the objections inherent in all quantitative tests which depend on fine distinctions of color, and the figures can not, of course, be looked on as other than approximate. In control tests, with solutions of pure bilirubin, we have found, however, that the limit of the reaction corresponds, quite uniformly, with a dilution of about 1 to 40,000 when read at the end of half an hour, and that a distinction between such dilutions as, say, 1 to 32,000 and 1 to 35,000, can be made without difficulty. In the application of the test one possible source of error has been encountered. In the very few cases in which we could demonstrate a considerable amount of urobilin in the blood (but no bilirubin) this test gave a peculiar smoky purplish color at the point of contact which by careful inspection, however, was readily distinguishable from the blue ring of bilirubin.

We have found, with Gilbert and Herscher, that a faint blue ring is present, usually, in undiluted normal blood serum, and that it is indistinguishable from that obtained in control tests with very weak bilirubin solutions. We are, therefore, inclined to agree with these writers, that the blood normally contains a minute quantity of bilirubin, although we have not yet obtained positive proof of this fact.

The test, we believe, is of distinct clinical value. Slight grades of jaundice and fluctuations in jaundice, which are quite imperceptible to the eye, are readily detected and measured. We have several times seen it of service as an aid in distinguishing between appendicitis and cholecystitis. In the differentiation of gallstone attacks from gastric or renal affections it seems likely to be of help, although we have as yet had no opportunity to try it.

The time required for making the test is not great and the chief obstacle to its general use is the difficulty of obtaining a sufficient quantity of blood. This difficulty, however, we have found to be much less than might be supposed, and in hospital practice at least the blood can be obtained with very little trouble. The method used by us is as follows:

After the upper arm has been bound so as to obstruct the venous return and the skin about the front of the elbow has been made aseptic, a sterile aspirating needle of medium size is thrust through the skin over the median cephalic or basilic vein, and then, with a second slight thrust, is made to penetrate the vein. From 15 to 30 c.c. of blood are al-

lowed to flow directly into a clean, large test-tube, and then the arm ligature is removed before the needle is withdrawn. If the needle is bright and smooth and the procedure is done briskly, the blood will usually flow freely, and there will be no clotting in the needle. The tube of blood is allowed to clot in the open air and is then placed on ice to permit the serum to separate. This separation may be hastened somewhat by placing the tube for a short time in a thermostat. The yield of clear serum is usually 40 to 50 per cent. of the volume of whole blood.

II. THE RELATION OF UROBILINURIA TO BILIRUBINEMIA.

In connection with their studies of the bilirubin content of the blood serum in various diseases by the method just described, Gilbert and Herscher[7] investigated the condition of the urine with regard to urobilin. They found that in all cases in which the urine contained pathologic amounts of urobilin, or its precursor, urobilinogen, the blood regularly showed a pathologic amount of bilirubin. They were not able, however, to demonstrate urobilin in the blood, even when it was present in the urine in very large quantity. The constant relation between bilirubinemia and urobilinuria, the absence of urobilin from the blood, and the results of certain experimental work led them to believe that the urobilin which appeared in the urine was not simply the result of the excretion by the kidneys of urobilin carried to them by the blood, but was actually produced in the kidneys themselves, by a process of reduction from the bilirubin of the blood, and that urobilinuria was, therefore, only the index of a cholemia.

This theory of the renal origin of the urinary urobilin had been suggested by von Leube[8] many years before, as a result of his findings in a case of jaundice in which the urine showed only urobilin, whereas the sweat, obtained by pilocarpin injections, contained only bilirubin. Von Jaksch[9] also was inclined to accept this view of the origin of urobilinuria, as were certain Italian investigators (Patella and Acorimboni,[10] Mya[11]).

Ever since the discovery of urobilin by Jaffé[12] (1868) much uncertainty and much difference of opinion have existed concerning both its origin and its clinical significance. It is known to occur in the urine

7. Gilbert and Herscher: L'urobilinurie, Presse méd., 1902, x, 843. Also Herscher: Origine rénale de l'urobiline. Thesis, Paris, 1902.

8. von Leube: Beitr. zur Lehre von Urobilinikterus, Sitzungsb. d. phys. med. Gesellsch. z. Würzburg, 1888, p, 120..

9. Von Jaksch: Ztschr. f. Heilk., 1895, xvi, 48.

10. Patella and Acorimboni: Rev. clin., 1891, 465.

11. Mya: Arch. ital. di clin. med., 1891.

12. Jaffé: Zentralbl. f. d. med., Wissensch., 1868, vi, 241.

in a great variety of pathologic conditions[13] and to be present often in small amount in normal urine which has stood for some hours in the light. In freshly passed normal urine, however, urobilin itself is not found (Saillet[14]). There has been much discussion, also, over the relationship between the urobilin of the urine, the stercobilin of the feces and a body, having the same characteristics, which Maly obtained by the reduction of bilirubin and named hydrobilirubin. Although complete agreement is still lacking, the weight of evidence is strongly in favor of the identity of these three substances. The attempts also of Mac-Munn,[15] Jolles[16] and others to distinguish between "physiologic" and "pathologic" urobilin, chiefly on the ground of slight spectroscopic differences, seems to be without justification (Garrod and Hopkins,[17] Hildebrandt,[13] Huber[18]).

It was early noticed that many urines which were light colored when passed and gave no reaction for urobilin, after standing a few hours in the light, would grow darker in color and present the characteristic reactions of urobilin. The conclusion was natural that such urines must contain some colorless chromogen which, by the action of light, was gradually converted into urobilin. Such a colorless body (urobilinogen), which, when acted on by sunlight, was convertible into urobilin, was produced by Hoppe-Seyler[19] by the strong reduction of hemoglobin, and by Disqué[20] by a similar reduction of bilirubin. The change of urobilinogen into urobilin was shown by Disqué to be a process of oxidation. Further valuable information concerning the chemical nature of urobilinogen was furnished by Nencki and Zaleski,[21] who were able to produce it from hematin. They found that it had the formula $C_8H_{12}N$ and gave the pyrrol reaction, and they named it, therefore, hemopyrrol.

Further evidence of the pyrrol nature of urobilinogen has recently been supplied by Neubauer.[22] Moreover, it has been shown by various

13. For details of the clinical aspects of urobilinuria see article of Hildebrandt: Studien über Urobilinurie und Ikterus, Ztsch. f. klin. Med., 1906, lix, 351.

14. Saillet: Rev. de méd., 1897, xvii, 109.

15. Mac Munn: Jour. of Physiol., 1890, x, 71.

16. Jolles: Zentralbl. f. inn. med., 1895, xvi, 1161.

17. Garrod and Hopkins: Jour. of Physiol., 1896, xx, 112.

18. Huber: Ueber die Ursache und der Bedeutung der Urobilinurie, Charite-Ann., 1906, 49.

19. Hoppe-Seyler: Ber. d. deutsch. chem. Gesellsch., 1874, vii, 1065.

20. Disqué: Zeitschr. f. physiol. chem., 1878, ii, 259.

21. Nencki and Zaleski: Ber. d. deutsch. chem. Gesellsch., 1901, xxxiv, 997.

22. Neubauer: Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol. in München, 1903, ii, 32.

investigators that urobilinogen occurs in the urine, feces and bile under the same conditions as, and usually in association with, urobilin.

Since there is now general agreement that urobilinogen is simply a precursor of urobilin and has the same source and the same significance, we shall, for the sake of convenience, in what follows, use the term urobilin to include both urobilin proper and urobilinogen, unless it is made evident from the context that the term is used in its more restricted sense.

The renal theory of the origin of urobilinuria, so vigorously advocated by Gilbert and Herscher, while attractive and plausible, is yet so contrary to the generally accepted views that it has seemed to us desirable to verify, if possible, the assertions of these investigators that urobilinuria occurs only when an abnormal quantity of bilirubin is present in the blood, and that, even when urobilin is abundant in the urine, it can not be found in the circulation. Moreover, it was desirable to know if anything like a quantitative relationship could be established between the urobilin in the urine and the bilirubin in the blood, as one might reasonably expect if the former were merely the result of the latter.

With these objects in view we have, in most of the cases in which the bilirubin content of the blood was determined, examined the urine simultaneously for urobilin. In many of the cases, also, urobilin has been sought for in the blood.

Before giving the results of these investigations it is necessary to describe in some detail the methods employed, since the conflicting results of different writers, especially those relating to the demonstration of urobilin in the blood, seem to be due, in large part, to differences in method and technic.

Methods Employed.

For the demonstration of bilirubin and urobilin in blood serum we have relied chiefly on Hedenius' and Syllaba's methods, the latter slightly modified.

Hedenius' method:[23] This consists in the precipitation of from one to three c.c. of serum with two volumes of 95 per cent. alcohol, acidification with 5 drops of 10 per cent. hydrochloric acid and filtering, after having heated twice to boiling. Filtrate and sometimes precipitate, are green in the presence of bilirubin.

Syllaba's modification of D. Gerhardt's method:[24] "About 5 c.c. of serum is doubly diluted with water and coagulated with the addition of sodium sulphate and acidification with acetic acid. The bilirubin will be completely carried down by the coagulated albumin, while the urobilin will remain in solution. Filter. In order to make sure that coagulation is complete the filtrate is boiled. If there is no urobilin present, the filtrate is clear, colorless, and spectroscopically free from the absorption band. If urobilin is present the filtrate is reddish colored and shows spectroscopically a fine stripe between C and F. The precipitate col-

23. Hedenius: Malby's Jahresberichte, 1894-5, xxiv, 385.
24. Syllaba: Folia hæmatologica, 1904, I, 636.

lected on the filter-paper is white in the absence of bilirubin but is of a pale yellow color if it is present. The precipitate is then washed with hot water, boiled with alcohol acidified with sulphuric acid and filtered. In the presence of bilirubin the alcohol is colored a bright green and the precipitate on the filter paper is also green. In the absence of bilirubin the alcohol is colorless and the precipitate is white."

In working with Syllaba's method we found that frequently some of the urobilin was carried down with the precipitated albumin and appeared only in the filtrate obtained after the precipitate had been boiled with acid alcohol. On this account we slightly modified Syllaba's procedure as follows: 5 c.c. clear serum, diluted with 10 c.c. distilled water, were coagulated by short heating in water bath after the addition of about 0.5 gm. powdered sodium sulphate and 1 c.c. of 5 per cent. acetic acid. The filtrate from this was either practically colorless or faintly yellow or faintly pink. The color of filtrate, we found, could not always be taken as an index of the presence or absence of urobilin and all filtrates must be carefully examined spectroscopically after the addition of two or three drops of Lugol's solution. We employed a large spectroscope and absorption cells from 1 to 4 cm. in depth. (A small pocket spectroscope gives fairly satisfactory results if filtrates are clear.) After neutralization, the filtrate was tested with Schlesinger's zinc acetate solution for confirmatory green fluorescence. This was allowed to stand twenty-four hours before being pronounced negative. The precipitate, usually very faintly yellow or white, was boiled in water bath a few minutes with 20 to 30 c.c. of 5 per cent. acid alcohol (hydrochloric acid 5; 95 per cent.; alcohol, 95). The filtrate from this was sometimes colorless, sometimes green, sometimes yellowish pink. The colorless filtrates contained neither urobilin nor bilirubin. The green filtrates contained bilirubin, and on spectroscopic examination occasionally showed a band of urobilin. The pink filtrates contained only urobilin. Syllaba does not mention the possibility of obtaining a pink acid alcohol filtrate, so it is probable that he had no opportunity to work with sera containing as large quantities of urobilin as those we encountered.

The confirmatory green fluorescence may readily be obtained, after neutralization, in the pink filtrates, but this reaction is not so satisfactory in the green filtrates, as biliverdin will give a confusing fluorescence. This fluorescence of biliverdin with zinc acetate solution in our experiments, seemed to bear a direct relation to the amount of biliverdin present. Occasionally the precipitate from 5 per cent. acid alcohol is green, at other times pearly white or pearl blue. A further boiling of this precipitate with 20 per cent. acid alcohol will yield a filtrate similar to that obtained with 5 per cent. acid alcohol if the amount of pigment was originally large. The sera in which by this method we were able to demonstrate urobilin only, and no bilirubin, gave after coagulation an almost colorless, or faintly yellow or pink filtrate as described above, showing characteristic absorption band and giving fluorescence with zinc acetate. The precipitates from these sera were bluish-white and on boiling with 5 per cent. acid alcohol they gave a pink filtrate showing an absorption band, and fluorescence with zinc acetate. In the specimens showing large amounts, reboiling with 20 per cent. acid alcohol gave a similar but much fainter reaction. No green filtrate could be obtained.

Ehrlich's para-dimethyl-amido-benzaldehyd reagent (2 per cent. solution in 5 per cent. hydrochloric acid) gave a positive reaction in three of our cases. In two the characteristic red color developed immediately and in the other after fifteen minutes. As shown by Neubauer,[2] this substance reacts to all bodies containing the pyrrol ring. That in these cases the body responsible for the reaction was urobilinogen was readily shown by the demonstration of the absorp-

tion band of urobilin, as well as that of the benzaldehyd, on the completion of the reaction.

Attempts to separate the urobilin directly from the serum by means of amyl alcohol were unsuccessful because of the tendency to the formation of an emulsion, from which the alcohol separated very slowly and incompletely.

Braunstein's[25] test was found inapplicable, failing in several sera known to contain urobilin. It gave a positive pink chloroform extract in one serum in which all other tests for urobilin were negative.

Schlesinger's direct application of his zinc acetate test without previous coagulation gave a positive fluorescence and band in one case in which we had previously demonstrated urobilin. Blood is received directly into a 0.5 per cent. solution of calcium oxalate in 200 c.c. 0.7 per cent. sodium chlorid solution and corpuscles separated by centrifuge. The zinc acetate solution is added to the resulting fluid. The possibility of bilirubin giving rise to a deceptive fluorescence should be borne in mind and results confirmed by spectroscope.

Urobilin and bilirubin in urine: The characteristics relied on for the demonstration of urobilin in the urine were its absorption spectrum, a single band between C and F near F and the green fluorescence developing in the presence of certain zinc salts. The chromogen urobilinogen has no characteristic spectrum but it is readily, and apparently quantitatively, converted into urobilin by the addition of a few drops of Lugol's solution. The fluorescence may be readily developed by the addition of an equal volume of a 10 per cent. solution of zinc acetate in absolute alcohol as suggested by Schlesinger. This is a simpler and more sensitive method than the older one in which zinc chlorid and ammonia were used. Ehrlich's benzaldehyd reagent was not used for demonstration of urobilin because the many substances containing the pyrrol ring which may occur in the urine necessitate the spectroscopic confirmation of each positive reaction.

For the quantitative estimation the simple method was used of diluting the specimen to the point of disappearance of the absorption band when observed in a layer 1 cm. deep. The complete daily volume of urine was not taken into account in these estimations. (The highest value we encountered in this series required a dilution of 100 times before the disappearance of the band.)

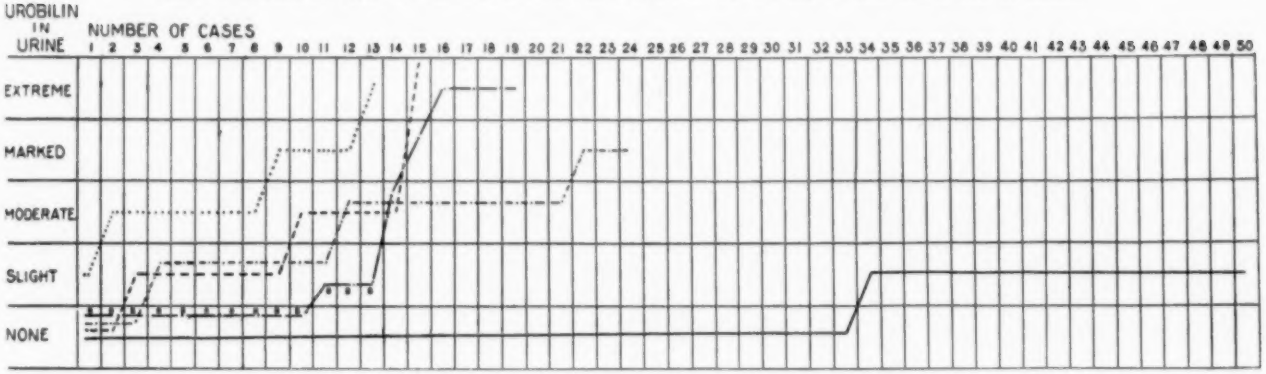
For the demonstration of bilirubin Huppert's test and its various modifications were sometimes used, as was also Hedenius' test, but we relied chiefly on Rosenbach's modification of Gmelin's test. For this several sheets of soft Swedish filter-paper were used and a large volume of urine slowly filtered through them. On the pigment thus collected a drop of yellow nitric acid gave the most satisfactory play of colors.

Simultaneous quantitative examinations of the blood serum for bilirubin and the urine for urobilin were made in 121 cases. The results of the examinations of the urine have been grouped into five classes, according as urobilinuria was absent, slight, moderate, marked or extreme. Similarly the results of the examinations of the blood for bilirubin have been divided, arbitrarily, into five groups, representing different degrees of bilirubinemia.

The mutual relations between the two series of groups can best be appreciated by their graphic representation, as in the accompanying chart.

25. Braunstein: Ztschr. f. Krebsforsch., 1903, i, 15.

CHART SHOWING RESULTS OF EXAMINATION OF BLOOD SERUM FOR BILIRUBIN AND URINE FOR UROBILIN.



			From	To
Group 1.	————————	Bilirubin concentration in blood serum.....	1 to 35,000	1 to 40,000 or negative.
Group 2.	- - - - - - - - - - - - - - -	Bilirubin concentration in blood serum.....	1 to 30,000	1 to 35,000
Group 3.	—.—.—.—.—.—.—.—	Bilirubin concentration in blood serum.....	1 to 20,000	1 to 30,000
Group 4.	.....	Bilirubin concentration in blood serum.....	1 to 10,000	1 to 20,000
Group 5.	——.——.——.——.—	Bilirubin concentration in blood serum.....	1 to 1,900	1 to 10,000

Considering, first, the group of cases (50 in all) in which the bilirubin content of the blood may be regarded as normal (1 to 35,000 or less), it will be seen that the urine was entirely free from urobilin in two-thirds of the cases and that in all the remaining ones urobilin was present in only slight amount. A study of Groups 2, 3 and 4 will show that, as the bilirubin content of the blood increases, there is also a steady rise in the average of urobilin in the urine, although the individual cases of each group show well-marked variations in the degree of urobilinuria. Group 5, however, which contains the highest grades of bilirubinemia and represents the cases of marked jaundice, shows a striking departure from this general rule. Of the 19 cases included in it, 10 showed no urobilin in the urine and 3 others only a small quantity, but in all of these 13 cases the urine gave a strong reaction for bilirubin (indicated by the letter B in the chart). In the remaining 6 cases of this group the urine contained very large quantities of urobilin, but no bilirubin. (It should be added that in no other cases of the entire series was bile pigment found in the urine.)

It has long been known that in many of the severest cases of jaundice the urine is entirely free from urobilin. The usual explanation for this peculiarity is that in such cases there is complete occlusion of the common or hepatic duct and, because no bile can enter the intestines, no urobilin (stercobilin) is formed. Indeed, it is just this class of cases that has furnished one of the strongest arguments of the supporters of the theory of the enterogenous origin of urobilinuria. Gilbert and Herscher attempt to harmonize these facts with their renal theory by supposing that, when the concentration of bilirubin in the blood reaches a certain point the kidneys are, as it were, overwhelmed by it and are no longer able to convert it into urobilin and that, therefore, bilirubin passes unchanged into the urine.

If we except the cases just referred to, it is evident from the chart that a very close relationship between bilirubinemia and urobilinuria does exist. When the bilirubin content of the blood is normal, urobilin is either absent altogether, or is present in the urine only in very small quantity. With the increase of the bilirubin concentration there is a well-marked tendency for the urobilinuria to become more and more pronounced. But this quantitative relationship is by no means apparent in every case. In each of the Groups 2 and 3 there are two or three cases in which the urine contained no urobilin at all. On the other hand, the last case in Group 2 showed a degree of urobilinuria greatly in excess of that of the other cases of that group. It is evident, therefore, that, while it may be stated as a general rule that bilirubinemia and

urobilinuria go hand in hand and usually bear a rough quantitative relation to each other, the exceptions to this rule are so frequent and important that it can hardly be said to furnish much support to the renal theory of the origin of urobilinuria.

III. UROBILIN IN THE BLOOD.

Very conflicting opinions have existed concerning the presence of urobilin in the blood. Herscher,[7] in 55 examinations in cases of marked urobilinuria, was never able to demonstrate it; and these negative results were used to support the renal theory of urobilinuria. Schlesinger,[26] using better methods, failed, in 15 cases of marked urobilinuria, to detect urobilin in the blood, and endorses the views of other writers (Gerhardt, F. Müller), that, in fresh blood, urobilin in any considerable quantity does not occur. On the other hand, Huber[18] states that in the 40 cases examined he was always able to find urobilin in the blood when it was present abundantly in the urine. He ascribes Herscher's negative results, and his own earlier ones, to the use of unsatisfactory methods. He insists that with Schlesinger's method its demonstration in the blood is easy. It is necessary to convert the urobilinogen into urobilin by adding one or two drops of Lugol's solution, and this, he thinks, is probably the reason why Schlesinger himself failed to find it. Biffi,[27] in a very recent article, states that urobilin (or its chromogen) can be demonstrated not infrequently in the blood and that in certain diseases, e. g., croupous pneumonia, it is to be found "almost always" in considerable amounts.

Our own experience does not tally exactly with that of any of the writers cited. In spite of repeated and careful efforts, in patients with marked urobilinuria, our results were uniformly negative until we chanced to examine blood serum from a patient with a very severe case of lobar pneumonia with beginning pulmonary edema, on whom venesection had been done. The results in this case were in striking contrast to those of our other cases. Urobilin could be demonstrated readily by every method and could be easily measured by the spectroscope. In 9 other cases of the same sort—patients with very severe pneumonia who soon afterward died—exactly the same results were obtained. (In several of these cases urobilin was present in such quantity that the untreated blood serum showed a pronounced green fluorescence.) In these

26. Schlesinger: Zum klinische Nachweis des Urobilin. Deutsch. med. Wchnschr., 1903, xxix, 561.

27. Biffi: Ueber das Vorkommen einer bedeutenden Menge von Urobilin im Blute menschlichen Leichen, Folia hæmatologica, 1907, iv, 533.

cases there was nothing in the urobilin content of the urine to distinguish them from many other pneumonias. While the urobilin was abundant in the urine (the dilution values varied between 6 and 40), it was less in amount than in several cases of pneumonia which showed no urobilin in the blood, and was much less than in certain cases of cirrhosis in which, likewise, the blood failed to show urobilin.

Another surprising fact in these 10 fatal cases of pneumonia was that, while urobilin was present in large amount, no bilirubin could be found in the blood. In 3 severe cases of pneumonia in which the patients eventually recovered, the blood contained a small quantity of urobilin and also some bilirubin. Still another severe case showed only bilirubin on the first examination. On the next day the blood contained both bilirubin and urobilin. A day or two later the patient died, without another blood examination having been made. In contrast to the blood findings in these severe cases of pneumonia, there were 15 cases with recovery in which no urobilin could be demonstrated in the blood. In all but one of these the blood contained an increased quantity of bilirubin.

The constant appearance of urobilin in the blood in pneumonia patients shortly (from one to three days) before death seemed to present such a notable exception to the general rule (in our examinations) that no urobilin can be found in the blood, even when it is present abundantly in the urine, that efforts were made to find some explanation for this peculiarity. The apparent disappearance of bilirubin from the blood suggested the possibility that the growth and multiplication of pneumococci in the blood might bring about the transformation of the circulating bilirubin into urobilin. Another possibility was that, by the action of the bacteria, urobilin might be formed directly from the hemoglobin of the blood. Added plausibility was lent to this idea by the well-known fact that the growth of pneumococci in blood-containing media is often associated with the deveopment of a greenish color, as, for example, in the green-tinted vegetations in acute pneumococcic endocarditis. In order to determine these points, agar plates, to which had been added varying quantities of blood, were inoculated with pneumococci obtained from some of the fatal cases; a second series of plates was inoculated with *Streptococcus mucosus capsulatus* obtained from the patient in a fatal case of septicemia with pneumonia and urobilinemia. In addition, cultures of these organisms were made in bouillon and glucose bouillon to which had been added varying amounts of hemoglobin and bilirubin. In none of these cultures, however, could urobilin be demonstrated. A partial reduction of the hemoglobin was obtained, but no urobilin.

Rabbits were also inoculated—two with the pneumococcus and one with the *Streptococcus mucosus*—but their blood, although swarming with the bacteria, failed to show urobilin. Portions of consolidated lung from patients showing urobilinemia, when washed free from blood and ground in a mortar, likewise failed to show the presence of urobilin. We were, therefore, forced to the conclusion that the marked urobilinemia observed in the very severe forms of pneumonia is not to be explained on the ground either of bacterial transformation of hemoglobin or bilirubin into urobilin in the blood, or the formation of urobilin in the hepatized lung itself.

A recent statement by Biffi,[27] which has come to our notice only since the completion of this work, has a direct bearing on this subject. He found that postmortem blood almost invariably contained urobilin in considerable quantity. In 96 such examinations he could demonstrate urobilin in the heart blood in all but two cases, and these two were cases of sudden death in persons up to that time in good health. That the urobilinemia was due neither to a postmortem diffusion of the intestinal stercobilin nor to bacterial reduction of the plasmochrome (bilirubin?) into urobilinogen he thinks probable from the fact that it was found in cases examined a very short time after death. On the other hand, in several of his cases the blood had been examined for urobilin only a few days before death, with negative results. The condition was observed after death from all manner of diseases and at all seasons of the year. Biffi suggests, therefore, that the development of the urobilinemia occurs during the last few hours of life as an antemortem change, irrespective of the nature of the fatal disease. We have as yet had no opportunity to verify this view. In our cases of pneumonia, while there was regularly the appearance of a urobilinemia in the fatal cases during the last day or two of life, urobilin also appeared, in small amount, in three severe cases which ended in recovery. It can not, therefore, be purely an antemortem change. This subject will be referred to again later.

In the light of our own experience it is difficult to understand the statement of Huber, that he was always able to demonstrate urobilin in the blood in cases of marked urobilinuria. In over 60 examinations, most of them in cases with a high grade of urobilinuria, we were able to demonstrate urobilin in the blood serum only in the cases of severe pneumonia mentioned above. In these cases, however, the reactions for urobilin were so distinct and so easily obtained that it seems very unlikely that our failures in other instances were due to faulty technic.

We have found that the zinc acetate test (Schlesinger's), in the presence of bile pigment, is unreliable, as a distinct green fluorescence may

be produced by biliverdin. In blood serum containing bilirubin, therefore, reliance must be placed on the spectroscope and Syllaba's test. In view of the fact that Huber's results were obtained with Schlesinger's test, and the further fact that most cases of marked urobilinuria are associated with bilirubinemia, it seems probable that some of his positive reactions may have been caused by biliverdin rather than by urobilin.

IV. THE SOURCE OF URINARY UROBILIN.

A number of theories have been advanced to explain the origin of the urobilin of the urine, and much difference of opinion and uncertainty still exist concerning it. The subject is complicated by the fact that, as has been said, there is still some conflict of opinion concerning the identity of the urinary urobilin with the stercobilin of the feces, although the weight of opinion strongly supports the view that they are identical.

Briefly stated, these theories are as follows:[28]

The Hepatogenous Theory.—This has gained widespread acceptance in France, chiefly through the advocacy of Hayem[29] and his school, and is well defined in the dictum of Hayem: "L'urobiline est le pigment du foie malade." When the functional activity of the liver is disturbed the coloring matter of the blood is manufactured, not into bilirubin as usual, but into urobilin. Urobilinuria is, therefore, an indication of hepatic insufficiency. This insufficiency may be absolute, when the liver itself is at fault, or relative, when, owing to the excessive amount of blood pigment carried to the liver, this organ can no longer convert it all into bilirubin.

The Hematogenous Theory.—In this the blood itself, rather than the liver, is looked on as the direct source of the urobilin. Urobilinuria is known to occur with all sorts of blood extravasations and in various conditions in which there is extensive destruction of red cells, for example, in paroxysmal hemoglobinuria, scurvy, blackwater fever, pernicious anemia, sulphonal poisoning, etc. Moreover, urobilin has been found locally in blood extravasations, it (urobilinogen) has been produced by a process of reduction from hematin, and is said to have formed in a solution of hemoglobin which had been for a long time protected from bactericidal action (Winter).

The Histogenous Theory.—This has as its basis the fact that in many forms of jaundice, especially in conditions of fading jaundice, the urine

28. The whole question is discussed fully by Weintraub in von Noorden's Metabolism and Practical Medicine, Am. ed., 1907, ii, 241.

29. Hayem: Sur la valeur diagnostique et prognostique de l'urobiline, Gaz. d. hôp., 1889, lxii, 1314.

contains very large quantities of urobilin and no bilirubin. It was, therefore, assumed that the bilirubin deposited in the various tissues might, by the action of those tissues, be converted gradually into urobilin which, because of its great diffusibility, would be taken up promptly by the blood and excreted in the urine.

The Renal Theory.—This is really only the application of the histogenous theory to a particular type of tissue, and has already been referred to.

The Enterogenous Theory.—This assumes that the only source of urobilin in the body is the intestines, where it is formed in large quantity, and that urobilin appears in the urine when, for any reason, it is absorbed from the intestines in larger amount than usual.

Many facts, both clinical and experimental, support the view that a close relationship exists between the urobilin of the intestine and that of the urine. Urobilinogen and urobilin (stercobilin) are formed in large amount in the intestine by the reducing action of the putrefactive bacteria on the pigment of the bile. Urobilinogen is found chiefly in the small intestine, urobilin chiefly in the colon. Normally these substances are to some extent absorbed from the intestine and carried to the liver, where they are, in part at least, excreted in the bile. When no bile enters the duodenum, as in occlusion of the common duct, urobilin disappears from the intestine, bile and urine. In a case of this sort Friedrich Müller[30] found that by administering bile by mouth urobilin could be made to appear in the urine and that it disappeared soon after the feeding of bile ceased. Newborn infants during the first few days of life, that is, before putrefactive bacteria have invaded the intestine, show urobilin neither in the stools, bile nor urine. In many disturbances of the liver associated with marked urobilinuria, an unusually large quantity of bile pigment is furnished to the intestine (pleiochromia) and the conditions are favorable there for the production of an increased quantity of urobilin. These facts, on the one hand, and, on the other, the absence of convincing evidence that urobilin is produced elsewhere in the body, have led to the wide acceptance, especially in Germany, of the idea that the urobilin of the urine is produced in the intestine and is simply the expression of its increased absorption from the intestine. Increased absorption does not necessarily imply an increased production in the intestine. Ladage[31] has shown that when urobilin is introduced into the upper part of the small intestine most of it is absorbed and ap-

30. Müller (F.): Ueber Ikterus, Verhandl. d. schles. Gesellsch. f. vaterl. Kultur, 1892.

31. Ladage: Bijdrage tot de kennis der Urobilinurie, Thesis, Leyden, 1899.

pears in the urine. Conditions which favor the rapid conversion of bilirubin into urobilin in the small intestine might, therefore, be assumed to favor the absorption of the latter. Efforts to demonstrate a parallelism between urobilinuria and increased intestinal putrefaction, however, have thus far not been successful (Fischler[32]).

But the intestinal theory of the origin of urobilinuria fails satisfactorily to explain many of the clinical facts. There is abundant evidence, for example, that a marked urobilinuria may exist when it is certain that much less than the normal quantity of bile is entering the intestine. For these and other reasons which can not here be discussed, it seems very unlikely that conditions in the intestines constitute the sole, or even the chief, factor in the production of urobilinemia and urobilinuria.

The fact that normally the urobilin which is absorbed from the intestine is almost completely abstracted from the portal blood by the liver and returned to the intestine has led to the view that the failure of the liver properly to remove the urobilin brought to it by the portal vein may explain the appearance of urobilin in the general blood stream and in the urine. Such a failure might result from some disturbance of the liver itself, when only the usual quantity of urobilin was brought to it, or from the fact that the portal blood contained an amount of urobilin so great that even the normal liver was unable to abstract it all.

This combined intestinal and hepatic theory of the origin of urobilinuria seems at present to be the one which best explains most cases of urobilinuria. That it will, however, account for all cases of urobilinemia and urobilinuria is by no means certain. Of the several other possible sources it may be said first, that there is no proof whatever that urobilin is ever formed in the body tissues from the bile pigment deposited there. The renal theory, also, attractive and plausible as it seems, has little evidence to support it and fails to explain many of the clinical facts. We have shown that the relation between bilirubinemia and urobilinuria is not sufficiently constant to accord with such a view. It has been shown also that urobilin does occur in the blood. The theory, moreover, fails to explain satisfactorily the important class of cases of common duct occlusion in which, although bilirubin is present in the blood in large amount, no urobilin appears in the urine. Finally, the theory is contradicted by the experiment of F. Müller and by the later ones of Fischler,[32] in which perfusion of the living kidney with solutions of bilirubin failed to show any transformation of bile pigment into urobilin.

32. Fischler: Das Urobilin und seine klinische Bedeutung, Thesis, Heidelberg, 1906.

The view that urobilin may sometimes be formed directly from the hemoglobin of the blood can not be dismissed so readily. It is known that urobilin can be produced *in vitro* directly from hematin. There is at present, however, no proof that such a transformation occurs in the circulating blood. Our efforts to demonstrate such a source for the urobilinemia of certain cases of pneumonia were altogether unsuccessful. The possibility, however, of the hematogenous origin of urobilin must still be acknowledged.

Can the liver itself produce urobilin? And is there any basis for Hayem's dictum, that urobilin is the pigment of the diseased liver? A categorical answer to these questions can not be given at the present time. There are a multitude of clinical facts which point to the liver as the dominant factor in the production of urobilinuria. In no other class of disorders is urobilinuria so frequent and so excessive as in those associated with disturbances of the liver functions. In almost every variety of acute and chronic disease of the liver, urobilinuria is a common and conspicuous symptom. It seems probable that, in most such cases, this urobilinuria is caused by the failure of the disordered liver properly to arrest the urobilin carried to it from the intestine, and until within the past year or two no convincing evidence had been adduced to show that the liver, healthy or diseased, has the power of actually producing urobilin. Recently, however, Fischler,[32] in a series of interesting and carefully performed experiments, has obtained data which seem to prove that, under certain circumstances, the liver can, in fact, manufacture this substance. He found that in dogs, in which he had severed the common bile duct and had made a complete bile fistula and in which, therefore, no bilirubin could enter the intestine, the bile, which normally contains a considerable amount of urobilin, promptly became completely free from it and, at the same time, the stools became colorless and lost all but a small fraction of their urobilin. The urine also remained free from urobilin. He then produced changes in the liver by the administration of well-known liver poisons (amyl alcohol, phosphorus, etc.) and found that the bile immediately showed enormous quantities of urobilin and that urobilin appeared in the urine. With the subsidence of the poisonous effects, the bile and urine again became free from urobilin. In the face of these experiments it is difficult to escape the conviction that the liver can, under certain circumstances, produce urobilin.

How important a rôle this purely hepatogenous urobilin may play in the production of the clinical forms of urobilinuria and urobilinemia must be left for future study to determine. Fischler himself is inclined to believe that such an hepatogenous form of urobilinuria is exceptional.

It is possible, however, that these new facts may throw some light on the antemortem form of urobilinemia to which Biffi has called attention and which seems to correspond in most respects with the marked urobilinemia found during life in our cases of fatal pneumonia. When one considers that even in the extreme grades of urobilinuria it is usually impossible to demonstrate urobilin in the blood, it seems probable that the concentration of urobilin in the blood in these cases of pneumonia must have been exceptionally great—so great, indeed, that with the failing circulation of approaching death it is not easy to imagine the absorption from the intestine of a sufficient quantity of urobilin to explain it. In this connection reference should again be made to the striking fact that in these 10 cases of pneumonia with marked urobilinemia no bilirubin could be found in the blood, although it was almost constantly present in the other cases of pneumonia.

The constant association of these two exceptional conditions can hardly be a mere coincidence, and it suggests that both the marked urobilinemia and the absence of a bilirubinemia may have as a common cause the disturbed metabolism of a failing liver.

SUMMARY.

By a method devised and used extensively by Gilbert and his pupils we have made some 160 determinations of the bilirubin content of the blood serum in a variety of diseases, and have become convinced that this method of *cholémimétrie* is sufficiently simple and reliable for clinical use, and that by it one may readily recognize and measure slight grades of icterus which fail to disclose themselves either by discoloration of the skin or by the presence of bile pigment in the urine. The method has, we believe, a distinct field of usefulness as an aid in the differential diagnosis between affections of the bile passages and those of other organs, such as the stomach, appendix and kidney.

Simultaneously with the examination of the blood serum for bile pigment the urine was tested quantitatively for urobilin. The mutual relations between bilirubinemia and urobilinuria are shown in the foregoing chart. It will be seen that when the blood serum was normal as regards bilirubin, the urine either was free from urobilin or contained only minimal quantities. With the increase in the concentration of bile pigment in the blood there was, in general, an increase in the urinary urobilin. But this rule was by no means invariable. A number of important exceptions occurred, notably among the cases of marked jaundice (Group 5), in many of which no urobilin could be demonstrated in the urine; on the other hand, in some cases the grade of urobilinuria was extreme. Our results, in the light of these exceptions, seem, therefore,

to offer additional evidence against the view that the urinary urobilin is formed in the kidneys from the bilirubin carried to them by the blood and is, therefore, only an index of the degree of cholemia.

In sixty cases of urobilinuria, some of them of extreme grade, the blood serum was examined for urobilin, with uniformly negative results except in the case of a group of ten fatal cases of pneumonia in which, during the last two or three days of life, urobilin was present in the blood in considerable amount, although its quantity in the urine was by no means unusually large. In fifteen pneumonia patients who recovered no urobilin could be found in the blood.

Our efforts to show that the marked urobilinemia in the fatal cases of pneumonia was the result of transformation of the hemoglobin or bilirubin of the blood into urobilin by the action of the circulating bacteria were entirely unsuccessful, as was also the attempt to demonstrate urobilin in the hepatized lung tissue. These negative results, in connection with certain other facts and with some recent experiments of Fischler, suggest the possibility that in these cases the urobilin of the blood may have a direct hepatic origin.

53 East Forty-ninth Street.

NOTES ON PELLAGRA AND PELLAGRINS.*

WITH REPORT OF CASES.

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DEFINITIONS AND SYNONYMS.

Until the recent work of Searcy, in Alabama, and the epoch-making studies of Babcock, in South Carolina, pellagra had been practically unrecognized in this country, while it has been known and studied for nearly two centuries in the countries of southern Europe and the east, under the various names of *mal de la rose, mal de misère, mal de sole, risipola estiva, erythema endemicum,* Lombardian leprosy, *mal de la spienza, mal del padrone, Balordone, elephantiasis italica, dermatagra, maidismus, psychoneurosis maidica.*

The word, "pellagra," compounded originally from the Italian *pelle agra* (rough skin), was first used by Frappoli, of Milan, as descriptive of the most characteristic skin lesion in the course of the disease.

Pellagra may be defined as a systemic intoxication, associated always with the ingestion of maize or maize products and characterized by a triad of symptoms (gastrointestinal, cutaneous and neuropsychic), with marked tendency to seasonal recurrences, exhaustion and death.

The term "pellagrin" is derived from the above and applied to those affected with the disease, particularly when the mental or nervous symptoms predominate, and has been in use since 1835, when it was estimated that, of 500 patients then in the asylum at Milan, fully one-third were pellagrins.

Pellagrous insanity is that form of mental disturbance affecting pellagrins and has been recognized as one phase of the symptoms in the course of the disease almost as long as the disease itself; and, although a large proportion of pellagrins end their days in asylums in a condition of driveling wretchedness and dementia, yet there seems still a doubt in the minds of some as to the propriety of a distinct classification for the psychosis, and no less an authority than Krafft-Ebing, in his text-book on insanity, devotes only a few lines to a "so-called pellagrous insanity."

HISTORICAL DISTRIBUTION.

Pellagra is said to have been noted first in Spain, around Oviedo, in 1735, and was described by Casal in 1762 as it then existed in Asturias,

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where it is still most active in Spain, and whence it has spread throughout the north and central Spanish provinces.

About 1750 it appeared in Italy and soon overran the whole of Lombardy, where it still rages with great intensity among the peasant classes, "overworked, underpaid and underfed," and whose diet is almost exclusively maize of poor quality, "poorly cultivated, harvested before it is matured and carelessly stored in a damp state." Southern Italy and Sicily seem to be exempt, notwithstanding the common use of corn meal as an article of diet in these sections.

In 1833 pellagra was noted in Roumania, and in 1856 presented itself finally in Corfu, at which time the local cultivation of maize on that island was supplanted by that of grapes, and the inhabitants began to import their corn from Roumania, where inferior grades are grown as in northern Italy.

In 1893 cases were reported from Egypt and more recently still from Austria, Servia, Bulgaria, Asia Minor, India, Barbadoes, Mexico, South America and finally (1907) United States of America.

Among those whose works and writings have contributed to our knowledge of this condition and of its prevalence throughout the world, should be mentioned Strombio of Legnano, who was placed in charge of the hospital established there in 1784 by the Italian government for the especial benefit of pellagrins; Giambattista Marzari, who first (1810) called attention to the relationship between maize and pellagra, and Vincenzo Sette, who (1826) first stated that the main cause of pellagra was fungi, producing acid decomposition of the fatty oils in the corn. From this developed the theories of the so-called "zeist" and "toxizeist," which will be referred to later on. Another is Bellardini, who advanced the "verdet" theory in 1844, and Lombroso, whose work a few years later somewhat overthrew the same. Von Deckenbach, 1907, made an able research on the etiology of pellagra. In this connection the experiments of Tizzoni and Panichi, in the same year, are also worthy of mention. Tuczeck, in 1906, published a very able paper on the nervous symptoms, and along the same lines Gregor, in 1907, published his findings from the study of cases in the Buckowina Asylum during 1904-05. Finzi is the first, 1902, to give the subject of *psicosi pellagrosa* special consideration.

In the United States, Sherwell, 1902, described the first case of pellagra which he found occurring in a Portuguese sailor aboard ship in New York. In the same year, however, Dr. H. F. Harris, of Georgia, described a case of pellagra in a patient with hookworm disease, and in 1907 G. H. Searcy reported an epidemic of pellagra occurring in the

insane asylum for negroes at Mount Vernon, Alabama. Merrill, of Texas, also reported a sporadic case in that same year; but to Babcock, of the State Hospital for Insane at Columbia, South Carolina, belongs the credit for the most complete study of cases yet presented in this country, and for stimulating the observations of others in various sections. Until this time all authorities had denied the existence of pellagra in this country, and most of the text-books of general medicine or nervous and mental diseases dismissed the subject with few words. This, coupled with the fact that the cases generally occur in crowded asylums all too scantily officered with physicians to permit of the most careful work, no doubt explains, in great part, its tardy recognition. There undoubtedly have been many cases overlooked in the past, but the greatest danger to be avoided in the future is not so much the failure to recognize the conditions, but rather a too great eagerness to diagnose as pellagra many related disorders.

ETIOLOGY.

Intimately associated with the history of pellagra itself is the study of its etiology. That there is a close relationship between the eating of maize and the incidence of pellagra there can be no doubt; and since 1810, when Marzari declared that corn, and especially the poorer qualities of it, lacked sufficient gluten to make a good food (and was, therefore, the true cause of pellagra), interest has centered about maize and a study of its parasitology for an explanation of the symptoms produced.

That this cause could not lie in maize *per se*, or in good maize, was evident from comparison of the wide extent of Indian corn consumption and production and the relatively small area of the globe in which pellagra was found. This was also brought out vividly in the study of pellagra on the Island of Corfu. Although the disease was widely prevalent on the mainland and adjoining countries, no cases had occurred on the island before 1856, notwithstanding that the inhabitants, who were skilled agriculturists, made corn a large part of their diet. The first case reported from this island was in 1856, at which time the culture of grapes had largely replaced the culture of maize, and most of the latter food product was imported from Roumania on the north, a country noted for its indifferent agriculture and poor quality of corn, and where pellagra at that time was flourishing.

Vincenzo Sette, in 1826, was the first to declare that the main cause of pellagra was a fungus growing on maize and which, according to his theory, produced an acid decomposition of the oils or "zein" of the corn, and from this sprang the theories of the "zeist" and the "toxizeist."

The "zeist" asserted that the seed of the *Zea Mays* itself was pathogenic, while the "toxizeist" considered it pathogenic only in so far that injurious substances could develop on it under outside influences.

This latter seems to have been the most generally accepted theory, and most of the subsequent investigations have been along this line, notably those of Bellardini and Lombroso. To Lombroso belongs the credit of having developed the theory which subsequently became known as the "verdet" theory; on the other hand, the experiments of Lucksch at Leipsic, 1906, tend to show that an exclusive diet of corn-meal, even of good quality, when fed to animals (guinea-pigs, rabbits and dogs), over a long period of time, would produce emaciation, intestinal catarrh and, in the case of the pigs, loss of hair and flaccid paralysis, symptoms suggestive of pellagra.

Sturli reviews the subject in the same year, and concludes that "we have to deal with an intoxication, most likely exogenous," and that the toxic agent gains admission to the human organism with vegetable food. The suspicion that the primary cause of the condition is a toxic variety of hyphomycete appears well grounded, but is not yet conclusively proved.

Tizzoni and Panichi, last year, reported that in acute and rapidly fatal cases of pellagra (typhus pellagrosus) they recovered a specific germ in pure culture from the blood and cerebrospinal fluid (and in one case from organs). They describe its biologic, cultural and pathogenic properties, and claim to have produced by subcutaneous injection into guinea-pigs (which seem peculiarly susceptible) the clinical picture of pellagra, symptomatically and anatomically considered.

Constantin Von Deckenbach of Jena, in 1907, in further investigating the relationship between maize and pellagra, confirmed his former experiments and those of Tiraborchi (1905), and as a result is convinced that the fungus, *Oospora verticilloides* (Saccardo) which was found parasitic on the living maize plant and which produces a disease of the plant, is as important a factor in the production of pellagra as *Claviceps purpura* is in causation of ergotism.

Various others have attributed to different varieties of pennicillium and of aspergillus properties causative of the disease, and a review of the literature would support the statements of German and Italian authors that the disease is an intoxication due to chemical substances produced in the grain by parasitic micro-organisms together with certain toxins liberated from those organisms themselves in the intestinal tract of man.

Among other and probably less important causative factors of pellagra should be mentioned sunlight or actinic rays, which are considered by many of no small importance in the production of the skin lesions. Indeed, in unrecognized cases, it is doubtless true that "solar erythema" has been the diagnosis of and explanation for the lesions on the hands and face; and in my own experience this was one of the suggestions offered to explain the condition. That sunlight does exert some effect there can be no doubt from observation of the cases here reported, in one of which especially exposure of the patient, a negro, to strong sunlight was followed by an exacerbation of all symptoms, including the mental.

Closely associated with the effect of the sun rays should be mentioned the seasons and their influence on the recurrences or exacerbations. In the classical descriptions, one is struck by the mention of vernal recurrences as characteristic of the condition, with subsidence or even complete disappearance of symptoms in the fall and winter. But there is diversity of opinion as to the absolute regularity of this, and in the cases here noted there were exacerbations or recurrences in the fall also.

Racial differences appear to have little bearing, the negro and Caucasian both being affected. In countries where the disease has long been endemic, the Jews are said to have remained remarkably free. In this country most of the cases reported thus far have been among negroes, while at the Florida State Hospital, with approximately an equal census of whites and blacks, only one case has been observed among the latter.

Agricultural classes, as a rule, are most affected, yet no walk of life can be said to be exempt where damaged maize is eaten, and in the series here reported there is one patient from the legal profession.

Sex and age seem to exert but little influence in predisposing to this affection, men and women being affected about equally and cases having been reported for all ages.

Alcoholism and other debilitating conditions are of influence only in so far as they lower vitality and weaken bodily resistance.

PATHOLOGY.

This phase of the subject has been studied more or less thoroughly from the viewpoint of both general and special pathology. The changes in the skin are mentioned in most books on dermatology and are described by Stelwagon as congestion, pigmentation and thickening, with ultimate atrophy and thinning in the upper layers of the cutis.

In postmortem examination of patients dying from pellagra, one is at once struck with the extreme emaciation and absence of adipose tis-

sue. Fragility and brittleness of bone is also described and may be particularly noticeable in the calvarium. Atrophy and fatty degeneration in all organs is found; and, in addition, "brown atrophy" of heart muscle and excessive pigmentation of liver cells have also been described.

In the cerebrospinal system, the findings are all suggestive of a toxic origin for the disease, and are sufficiently characteristic to assure its identity and strengthen its claim to classification as primarily a trophoneurosis. Parhon and Papinian (1907) found marked changes in the large Betz cells of the anterior horn of the spinal cord, these changes being described as varying from "partial to complete dissolution of the fibrillæ, also atrophy of the nuclei and changes in the Nissl bodies." F. Tuczec (1906) believes that pellagrous insanity may terminate in true dementia paralytica, and summarizes the pathologic findings in brain and cord as showing all degrees of regressive changes, with chromolysis and vascular degenerations; and, in addition, a combined sclerosis of the cord, involving the postero-lateral and posterior columns. The posterior column degeneration in pellagra differs from that of tabes in showing no involvement of the posterior roots. Marinesca has called attention to the more intense injury of the gray matter as compared with the white, and Babes and Sion are credited with directing attention to the marked degeneration of cells in Clark's column. Von Neusser, comparing the findings in ergot poisoning with those in pellagra, notes that the cord pictures in all three are very similar, but that ergotism and tabes both show involvement of posterior roots, while these roots remain free and uninvolved in pellagra. Marie sees in the changes a poliomyelitis-posterior, with degeneration of the "endogenous fibers" of the posterior and lateral columns. Déjerine has described a neuritis and atrophy of the nerves to the skin, while Raymond found such nerves in similar conditions intact.

SYMPTOMATOLOGY.

The symptoms of pellagra may be described under three divisions: (a) cutaneous, (b) gastrointestinal, and (c) nervous or mental.

The first of these are more or less characteristic, not so much in appearance as in distribution, incidence and recurrence, and consist primarily of a peculiar erythema which gave its name originally to the disease. The discoloration, which is at first bright red, but quickly becomes bronzed or a dull brown, is noticed, as a rule, as a patch on the back of the hands, or in some cases the knuckles of the hands and fingers are alone affected. Symmetrical in distribution, of a reddish or coppery hue, the discoloration extends toward the wrist and down on the fingers,

but never reaches far beyond the wrist on the back of the arm, and never involves the plantar surfaces; the skin, which is often tense and shiny, gives the appearance of a burn or "scalding" from the sun or steam. Indeed, this is often the first explanation suggested for the phenomenon, and one might be misled were it not for the coincidence of the nervous and intestinal symptoms, which close examination and inquiry at this time will always reveal. The skin of the face, just beneath the eyes and on the malar prominences, as a rule, will also show similar patches about the same time, and these spread to coalesce on the bridge of the nose. The dorsum of the feet, point of the elbows and more rarely still the back of the neck on either side, always symmetrically arranged, are also sites for the appearance of the eruption in more severe or unusual cases. At this stage, if the attack is a mild one or the conditions favorable, the skin lesions may resolve and disappear, leaving only a roughened pigmented skin with branny desquamation, and this is the condition from which the disease has derived its name of pellagra, or "rough skin." More often, however, the condition advances, small blebs appear, swelling into larger bullæ filled with a serous or seropurulent fluid, which finally burst, exposing the red weeping layers of the dermic tissue below. Again, Nature may assert herself and healing take place, this time with a thin, smooth, shiny atrophic skin for repair, but the patient is now, as a rule, in the last stage of the disease, and frequently the broken skin resists all treatment and death ultimately ensues. Another striking feature of this picture is the almost total absence of subjective symptoms, the patients rarely complaining except in the earliest stages, when some smarting and "feeling of fulness" may give them some concern. The skin symptoms are, as a rule, the last to occur, but when once exhibited are almost certain to recur at more or less frequent intervals and with varying intensity as long as the disease persists.

Coincident with the cutaneous, or generally preceding them by an indefinite period, are the gastrointestinal symptoms. These consist at first of a troublesome diarrhea with some gastric pain, and are apt to mislead, particularly if examination at this time reveals the presence of such parasites as frequently coexist. As the disease advances the diarrhea becomes more persistent and profuse; loss of weight follows, stomatitis frequently develops and the patient takes to his bed. The diarrhea is, as a rule, serous in quality and rarely shows any blood, but in later stages may assume the character of a mucous colitis and show faintly blood-streaked threads. The stomatitis, if it occurs, as a rule, is most intense. Within the lips, the cheeks and about the gums, and particular-

ly on either side of the frenum of the tongue, are the patches, which resemble very much the lesions of the skin and slough off, leaving red, ulcerating or bleeding bases. Salivation at this time is profuse, and the tenderness or soreness of the mouth and throat interfering with deglutition the patient complains most bitterly and sits or lies on his couch, miserably drooling. The fetid odor of the breath and the foulness of the sloughs both contribute to the disagreeable feature of the disease at this stage.

The nervous and mental symptoms, which have a prominent place in the picture throughout the course of the disease, are really among the earliest, if not the very earliest, to appear and predominate in the so-called prodromal stage of the affection. These, however, are so slight, consisting of headache, malaise, with perhaps vertigo, muscular weakness and tremors, that they may be overlooked and not noted unless the patient is in a hospital or asylum and already under the physician's care and observation. In one of the cases here reported (a typical uncomplicated case of pellagra) mental symptoms early predominated of an anxious, melancholic type, followed by restlessness, confusion and (finally) hallucinations of sight and hearing, with active delirium. The nervous symptoms exhibited at the same time consisted of intense tremors, exaggerated reflexes, spastic gait and a tense, drawn condition of the muscles of the lower leg and calf, much resembling tetany, and which caused the patient to complain of the cramp-like pain. Among other mental and nervous symptoms mentioned are irritability, insomnia, refusal of food, suicidal tendency, defects of memory and impaired intellect; also paresthesias and anesthesias of the skin of hands and feet, with sensation of cold in the extremities.

While the mental and nervous symptoms of pellagra have always been recognized, Finzi, 1902, claims to have been the first to give the subject of *psicosi pellagrosa* special consideration. He considered the psychosis a type of amentia, the characteristic symptom of which was a confusion of ideas. This view was coincided in by Tanzi, but vigorously opposed by Vedrani, who emphasized the fact that *psicosi pellagrosa* runs its course frequently without marked disturbance of orientation or consciousness. Earlier observers (Lombroso, Warnock, Aubert) were satisfied to classify the psychic symptoms of pellagra simply as melancholia. That we have in pellagra a distinct psychosis dependent for its symptoms on the toxic action of the maize fungi on the nerve cells, I think there can be little doubt. That these symptoms are polymorphous, as are those also of the other toxic psychoses (alcohol, etc.), likewise there can be little question. Symptoms of melancholia may

Fig. 1.—Patient at asylum, Mombello, near Milan, Italy. Photograph illustrates eczematous condition of the back of hands.

Fig. 2.—Patient at State Hospital, Columbia, S. C. Photograph illustrates eczematous state of the hands, also slight malar discoloration. (These two photographs were kindly loaned to the author by Dr. Babcock, of the State Hospital, Columbia, S. C.)

predominate, or be replaced with types of mild confusion and mania, resembling thus manic-depressive types, but with terminal stages always showing dementia. But the whole taken in connection with the cutaneous and other lesions, all of which in the last analysis may be traced to trophoneurotic influences, presents a picture which can hardly be mistaken, and should be as distinctively characteristic as that of any of the other toxic dementias, lues, alcohol, etc.

DIAGNOSIS.

A typical case of the disease presenting the triad of symptoms, dermatitis, diarrhea and depression, occurring in a section where the disease is known to prevail, and where the history of a maize diet can be established, should present no difficulty, but in the prodromal stage, or where the cases are ill-defined and atypical, the matter may not be so easy.

Mild alcoholic intoxication may be suspected, especially in those whose daily habits include the ingestion of wines and small beers. The disease may suggest biliousness, as the earlier symptoms suggest very strongly that rather vague condition which ranks next to malaria as a catch-all for indefinite complaints. Scurvy may be easily confused with pellagra until the appearance of the cutaneous symptoms, when the diagnosis will usually clear.

Ankylostomiasis may be considered responsible for the symptoms, especially where the examination of the feces discloses ova and hookworms.

Addison's disease is sometimes suggested from the pigmentation of the skin often seen in the later stages.

The skin lesions may be considered a separate condition from the intestinal and nervous symptoms, and the diagnosis of eczema in some of its protean forms follow.

Pemphigus may be considered, especially if the cases are first seen in the later stages when vesicular and bullous alterations have taken place in the skin. Solar erythema likewise may be suggested, especially when the skin lesion is seen in the early or mild cases.

Dermatitis venenata or calorica have also been suspected.

Leprosy has been suggested in some instances, and the skin lesions simulating the anesthetic form of that disease led to the name, "Lombardian leprosy."

Ergotism may be suspected, but the gangrenous character of the lesions and their localization on finger-tips, nose, etc., will soon serve to differentiate.

There has also been described a pseudo or false pellagra, against confusion with which one is constantly cautioned. But it is very doubtful that such a classification should be allowed, and it is very possible that all such cases are but mistakenly diagnosed related conditions.

Dementia præcox, manic-depressive insanity, and the various so-called terminal dementias may be considered and lead to confusion of diagnosis from the psychiatric standpoint.

In any and all of the foregoing, further observation and the onset of fuller symptoms will generally serve to differentiate the true cases of pellagra, and with the triad of symptoms, including typical cutaneous lesions described above, the diagnosis will be made.

PROGNOSIS.

The death rate among pellagrins is notably large, especially in the acute or fulminating form of the disease, as was described for the epidemic in Alabama. Even when death does not occur in the first attack, recurrences are frequent, and, if the conditions are not improved, exhaustion increases and death finally follows with the second or third exacerbation. In most of the cases reported in this country, the patients have succumbed within a few weeks or months. In Europe, it is said, pellagra may endure for many years. In those patients in which the patient escapes death the mental deterioration is permanent and more or less marked.

Alcoholics are the most unfavorable subjects, and any intercurrent disease or condition which lowers body resistance and vitality will, of necessity, affect the prognosis badly.

Children are said to be affected more mildly than adults and to acquire more readily a resistance to the disease.

TREATMENT.

The question of treatment resolves itself into two divisions, prophylactic and curative. Of the latter, little can be said, as no specific medicinal agent has yet been discovered for this disease, and removal from unhygienic surroundings, and improvement of diet, are the best means we have of combating the condition.

Milk, externally and internally, was used by the earlier practitioners, following the observations of Bouchard, that the cowherders in pellagrous districts escaped the disease.

Arsenic and iron preparations have also been much used, and potassium bichromate, alone or combined with sublimate (Hoch) has been said to give good results.

Iodin undoubtedly exerts a beneficial influence on the cutaneous symptoms, if applied in early stages of erythema; likewise hydrotherapy is of much service in the treatment of mental and nervous condition. Silver nitrate has been found a valuable adjunct in the treatment of the stomatitis, but for the diarrhea little of value has been found, although opium in some form is generally used in efforts to control the same.

More recently, Boscolo-Bragadin and D'Ormea have recommended protargol in doses of one-third grain daily for the intestinal condition—a suggestion based, no doubt, on the work of Roux, who found that silver, even in minute quantities, was fatal to the aspergillus, which is said to bear a direct relation to the disease.

The serum treatment also has been tried, but further work along this line is needed and no doubt will be awaited with great interest.

CONCLUSIONS.

An analysis of the described cases below and review of the literature seem to justify the following conclusions:

1. Pellagra undoubtedly exists in the United States.

2. Whites are more susceptible than blacks. (This conclusion seems justified by the fact that in the institution from which these reports are taken all—both white and black—are under a common régime and partake of a common diet with similar hygienic conditions for both, so that each race may be considered subject to the same etiologic factors, and the incidence of the disease has been 3 or 4 in the white to 1 in the negro.

3. The sexes seem equally affected. While the cases here reported are all from among the men, yet there have been an equal number of cases observed among the women, on which we may hope for a report in the future, when inferences may be drawn as to the resistant power in the respective sexes.

4. Previous alcoholic history affected the prognosis badly.

5. Mental and nervous symptoms prevail throughout the disease.

6. The disease is difficult to diagnose in the prodromal stage.

7. The mental symptoms are of polymorphous character, but the picture as a whole is undoubtedly one of a distinct disease, and a definite psychosis may with propriety be recognized in the symptoms of pellagrous insanity.

REPORT OF CASES.

CASE 1.—*Patient.*—J. E. P., white, male, aged 40; married; the father of four children, all living and well, was admitted on May 10, 1906, with the diagnosis of dementia præcox. He was a gasoline motor engineer, painter and carpenter, a native of Staten Island, who had resided in Florida for twenty-one years.

History.—The patient's family history was negative. Several brothers and sisters were dead, but causes were unknown. He had always been fairly well except for "stomach trouble" for the past ten years. This was explained as a chronic indigestion with attacks of diarrhea, and some nervousness. He had been given to alcoholic excess but abstained under pledge in later years. He was an excessive coffee-drinker, also a heavy smoker. He was said to have had sunstroke (doubtful). He had been bitten on the finger twelve years before by a man, which seemed to "affect his mind" and make him nervous. He had had lues, six or seven months' treatment. He had been adjudged insane four times, and was committed in this instance because of irritability at home, inability to perform his usual duties because of mental condition and lassitude, and fear of an outbreak. His commitment papers state that he would laugh and cry at times, like a child, and seem very weak; be affectionate at times, and then again abusive and boisterous. His symptoms at the time of admission were rather negative.

Examination.—The patient was a slender man, height 5 feet 9 inches, weight 125 pounds, with a very dark complexion. The pupils were large and equal. The tongue was coated but protruded well in midline with no tremor. There was a suggestion of water-hammer pulse; accentuated pulmonic second, with first sound at apex softened and prolonged. The reflexes were all active; there was no Babinski. Sensation seemed good; no motor disturbances were noted.

Course of Disease.—The mental symptoms varied; periods of quiet alternated with periods of restlessness, there were slight disturbances of consciousness, with depression. The patient was melancholy or dejected in expression. The first cutaneous symptoms were noted in December, 1906, with improvement and disappearance about the middle of January, 1907. There was recurrence of skin trouble in exaggerated form in July and August, 1907. The patient's condition failed to respond to treatment; the lesions on the hand improved, only to recur again. Diarrhea became persistent; marked stomatitis ensued; and the patient took to his bed. Emaciation progressively increased until his death, Sept. 2, 1907, about six weeks about onset of the second attack.

CASE 2.—*Patient.*—G. M., white, male, a Swede, aged 45, married, and father of one child three months old, apparently healthy, was admitted April 18, 1908. He had been a farmer, carpenter and bricklayer; had resided in Florida six months and in the United States fourteen years.

History.—The patient's family history was negative; his parents were probably still living and well. The patient had always been subject to headache; was in a hospital in Michigan in 1894, complaining of chronic bowel and stomach trouble, also some kidney trouble. He denied alcohol and venereal trouble, but admitted exposure. He used no tobacco. He had been knocked down by a blow on the back of the head some time before he left Sweden. He had always been thin and a hard worker. He had had a previous similar attack in November, 1906, when he was taken "seriously sick," "legs gave away," he had vertigo, "twitchings of muscles," "cholera-morbus" (attributed to diet of hog liver day preceding); he lost only one day from work, but was sick for a week or two. He married on Dec. 25, 1907, at which time recovery is said to have been complete. He had no more illness until the present attack, except violent headaches, which, his wife stated, the patient complained of only on Sundays when he was idle; but she stated that she never "got to know him well;" he always seemed a little peculiar," melancholy, depressed, self-accusatory.

Present Illness.—This dated from July, 1907, almost a year before admission here, and began with diarrhea, no fever, no chill, no marked pain; no blood except following vigorous medication which he received at the hands of various physicians consulted. He obtained relief but suffered from gradually increasing

weakness and nervousness with irritability and mental depression. He stopped work in December, 1907, since which time he had been under treatment and unable to do anything. The skin trouble was first noticed on the backs of his hands about the same time as the diarrhea began, in July, 1907, and was attributed to the action of the sun and the chemical preservative of lumber with which he was working at that time. He was sent to us because of his inability to work, irritability at home, depression, and grave physical condition.

Examination.—At the time of admission the patient seemed almost *in extremis*. He was prostrate, pale and emaciated; his tongue was coated and ulcerated around the edges; it protruded well, with no tremor. The pulse was negative, vessel wall sclerotic and tender on pressure. The thoracic organs were negative, the abdomen sunken and tender on pressure. The glands were negative; the hands and fingers were affected with a chronic dermatitis. There was dark red discoloration on the skin of dorsum, with vesicles and pustules surmounting. The inflammation extended no further than the wrists. Reflexes were all present but with diminished activity. There was no Babinski, but marked swaying in Romberg; tenderness over all long bones, and the patient complained of general aching of the body. His expression was pained and his mental state was one of anxiety. He asked to have "bad taste" removed from mouth; seemed oriented as to time and place but failed to recognize the relations of those about him. He did not remember when he came here, thought he might have been here a week.

Course of Disease.—The patient's disease ran an afebrile course, with persistent diarrhea, increasing emaciation and weakness, until his death, May 12, twenty-four days after his admission. The cutaneous symptoms were relieved and just a few days before the end the skin over hands had completely healed, presenting the reddened, thin, smooth, atrophic skin of some scar tissue. The chief mental symptoms observed in his case were the marked loss of memory and the anxious melancholy.

CASE 3.—*Patient.*—S. R., white, male, aged 51, married, was admitted April 16, 1908, with the diagnosis of pellagra. He was the father of nine children, all living and well but one, which died in infancy. He was a Canadian; had resided in Florida five years, and in the United States most of his life. He had been a farmer and a stationary engineer.

History.—The patient's family history was negative and his own previous history negative except for some cardiac and stomach symptoms, indigestion and diarrhea. The patient denied alcohol and venereal infection. In 1892 he fell from a height on his head and was unconscious seventeen days, following which he remained for some time in an asylum in North Dakota. He stated that he never recovered fully, and suggested that that was at the bottom of his trouble now.

Present Illness.—The patient's wife believed that his mind was slightly affected by an attack of grip in 1888, and that he had never been normal since the accident in 1892. He had suffered ten years with chronic diarrhea. He was in the habit of eating plenty of corn-bread, but his wife stated that he had brought on the recent attack by eating as his sole diet raw oatmeal and soda biscuit and drinking hot water. His most marked mental symptom was impaired memory. The patient would start home but forget the way and have to sit by the roadside until it came to him again. Irritability, chronic grumbling and nervousness were also noted.

Examination.—At the time of admission the patient was greatly emaciated, anemic, weak, with very poor condition of teeth and gums, stomatitis and diarrhea, and "purpuric" blistered condition on backs of hands. The mental symptoms noted at that time were chiefly those of a psychomotor retardation, with

difficulty of concentration and very poor memory, especially for facts in the remote past.

Course of Disease.—The patient remained in bed for two weeks, during which time there was gradual amelioration of all the symptoms except the diarrhea, which was not entirely relieved until some time afterward. He was soon able to be out and about the verandas; but did not improve rapidly and seemed constantly depressed and anxious over his condition; complaining often of malaise and general weakness. On June 1 he was again in bed complaining of feeling "chilly," and on June 5 the erythema reappeared on his hands, and for the next week or ten days there were noticed an increase of his mental symptoms, with considerable confusion for a day or two, the patient frequently, and for no reason, removing clothes and placing them in water-closet, etc. About June 20 he was again up. The previous symptoms had disappeared and been replaced by euphoria, talkativeness and grandiose ideas. The patient thought that he had some great invention and was fabulously rich. This lasted only a day or two; and from that time on he began to improve physically and mentally. To-day he weighs over 130 pounds (increase from 99 pounds on admission), and is a quiet, complacent, cheerful man; a little slow in speech and gait, but ever ready in conversation, and showing but slight deterioration of intellect. He is still under observation.

CASE 4.—*Patient.*—S. W., a negro, male, aged 28, married, with no children, was admitted May 5, 1908, with the diagnosis of toxic psychosis (pellagra). He had been a farm laborer, working on a truck-farm, scattering fertilizer by hand.

History.—The patient's family history was negative. He was born in Florida, an illegitimate child, and raised as an orphan. He denied indulgence in alcohol and venery.

Present Illness. The patient described very well an attack of confusion with active delusions and hallucinations, which he experienced at his home just prior to commitment, and which followed an indefinite attack of typhoid fever for eight weeks, concerning which little could be learned save a predominance of intestinal symptoms and increasing weakness and emaciation, coexistent with an inflammatory condition of the skin over hand, face and feet, which was attributed to the action of the commercial fertilizer which he had been handling in his work.

Examination.—At the time of admission the patient was emaciated, rather fearful but well oriented and otherwise apparently normal except for the condition of the skin over the backs of the fingers, hands and forearm, extending almost to and including the backs of the elbows, which were black (the patient was a brown-skinned negro), hard, thickened, rough, scaly or crust-like in character. No subjective symptoms were complained of. The patient was placed on general tonics with ichthyol ointment applied to the hands and also to the face and feet, where similar lesions were symmetrically arranged.

Course of Disease.—The patient's condition improved steadily. The few remaining mental symptoms completely disappeared as also did the skin trouble. At varying intervals, however, since his admission, every month or six weeks, this patient has shown recurrence of mental symptoms characterized by anxiety, depression, and restlessness, succeeded in turn by shorter periods of euphoria. These are accompanied always by nervous symptoms, consisting of tremors and exaggerated reflexes. His last attack, which began just a month ago, with a slight fever, has proved more severe than usual, and was accompanied by slight diarrhea, which has rapidly increased to a severe and exhausting one, and is just now beginning to abate. About two weeks ago signs appeared on his hands in the form of typical erythema, symmetrically arranged on the backs of the hands and feet, quickly involving also the skin of the elbows and beneath the eyes.

The appearance of these lesions on the negro's skin has seemed to offer slight differences from that on the white skins, in that the increase in pigmentation and the abnormal thickening are both greater. Otherwise, the character of the lesion is the same, progressing on to bleb formation with exfoliation and repressive changes or subsequent healing and persistence of an atropic reddened skin, in which state this patient's hands are to-day. The salivation and stomatitis which have been most severe, and only just now begun to heal, followed some time after the appearance of the skin lesions; and it is also worthy of note that the latter supervened only after exposure of the patient to direct rays of the sun while he was receiving a sun bath daily at one time. He complained so of the burning and smarting of the skin where it was affected, that he was removed into a room with no sunshine and the cooling effect seemed so immediate as to suggest the relation of cause and effect. Extract of opium to control the diarrhea, warm baths for the nervous symptoms, and silver nitrate (solution and stick) for the mouth, have been used; and the diarrhea has improved, the skin lesions healing, and the stomatitis disappeared almost completely. There remain but the nervous symptoms (tremors), tetanic condition of the feet, legs and exaggerated reflexes, to be overcome; then we may look forward to another interval of rest until possibly next spring. The mental symptoms which were very marked in this attack consisted at first of melancholy, confusion followed rapidly by delirium with active delusions and hallucinations. There has been a slight daily rise of temperature throughout this attack. This condition is still present, and the urine shows abundant casts and much albumin. The patient is still under observation.

CASE 5.—*Patient.*—J. B. C., white, male, a native of Florida, aged 57, married, admitted August 2, 1908, with a diagnosis of alcoholic dementia. He was the father of six children, one dead in infancy, one dead of typhoid.

History.—The patient's family history was negative. The patient had always been a steady and heavy drinker, though rarely intoxicated to such an extent as to interfere with practice of his profession.

Present Illness.—This had been coming on for eighteen months preceding admission, following soon after the death of the patient's favorite son. He gave up, became apathetic, remained in bed much of the time, and latterly all of the time; could not be controlled, and refused food. He had delusions of impending ruin for his family, and later developed somatic delusions regarding himself; said that his bowels had been removed by operation and that he was dead.

Examination.—On admission the patient's condition was one of great weakness, emaciation, constipation and melancholic depression, with pyschomotor retardation and irritability; he was inclined to mutism; and had delusions of persecution. His tongue was coated and protruded hesitatingly. There was a slight tremor of the fingers. The pulse was weak and small in volume; the vessels sclerotic. Heart sounds were weak, faint with slight thrills and murmur, systolic in time and heard all over the upper chest and in the axilla. The liver was enlarged and the edge plainly felt; hard. The abdomen was sunken. The glands were small, shotlike in the groin, axilla and neck. Venules were prominent over face and nose (from chronic alcoholism). Reflexes were all sluggish except knee-jerks and vasomotor which was prompt and pink. Sensation to touch was good. There was a slight speech defect. Dynamic power was reduced. There was no ataxia or incoordination, but a slight tremor.

Course of Disease.—Patient's disease ran an irregular course. His mental condition cleared up considerably so that he responded promptly to questions, though in a dull, listless way; he showed good insight, complained of mental impairment and particularly memory defects, which he said had been coming on for two years, and which he attributed to alcoholic excess formerly indulged in.

Slight alterations in temperature were noted while the patient was in bed, but this seemed to become regular and the patient was allowed to be up and about, even going at times to the recreation yard. There was constantly, however, a great lassitude, nervous twitching of the muscles around the mouth; untidiness, and melancholia. A slight diarrhea (which was attributable to laxative treatment) set in and the patient became very careless in his habits, frequently soiling his person. There was also noticed a favorite posture of the patient, with his hands held inside trouser and constant choreic or spasmodic movement of the fingers as if scratching the skin of the lower abdomen and thighs. He would give no explanation for this but persisted in it, and to it was attributed the first skin symptoms which appeared about September 6. He was put to bed and found to have fever of a low remittent type, associated with a continuance of the loose stools and some stomatitis. The mouth symptoms cleared up and the fever disappeared in about a week, but the lesions on the hands and face (his feet never became affected) became more chronic, and hands were not entirely clear from bullæ and exfoliation until the 23d, about two weeks after the onset, when the skin presented the typical thin, atrophic scarred condition. The intestinal symptoms, while improving also, never entirely subsided, and, although he was up and about the ward for the greater part of October, his stools were never less than two or three in the twenty-four hours; and while the mental symptoms also cleared up remarkably, with disappearance of much of the depression and retardation, he continued more or less untidy, frequently soiling himself at night, and excusing the untidiness on account of lassitude. His diet was extended, and about a week ago, following ingestion of ice cream, the diarrhea symptoms set in again, with great intensity and persistence, and the patient declined steadily with failing strength until death on the evening of Nov. 7, 1908.

In the preparation of this article I wish to acknowledge indebtedness to various text-books consulted on mental and nervous diseases, general medicine and dermatology; also to courtesies of the Surgeon-General's office and to Dr. C. A. Pfender in making abstracts. The following authorities:

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FEVER.*

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From the earliest times fever with all its remarkable symptoms has been familiar not only to physicians, but even to the general public, and the term is one so honored by age and by the good that must consequently inhere in it, that it can not be discarded or dismembered. It is, nevertheless, very difficult to define this conception clearly because even yet we are unable to say with certainty at what point the direct effects of the cause of the disease end and what really belong to the fever. For, although the elevation of the body temperature is one of the most salient points, it is by no means the only characteristic nor is it itself always to be regarded as an infallible sign of fever, for such elevation of temperature may occur in a perfectly healthy person, if, for example, he be immersed in a hot bath. There are other readily recognizable signs of fever, such as thirst, and weakness, and alterations in the character of the urine, but it is difficult, indeed, to be sure of what part of each of these is produced by the bacterial poisons that cause the disease, what part by the fever itself. Kraus,[1] in his recent review, has, on this account, written of fever and infection together.

It is clear, from the fact that the ideas that prevail as to its general character are so uniform throughout the world, that, no matter what the nature of the disease that brings fever with it, the fever itself is the same. Sometimes it is ushered in with a chill, sometimes it begins gradually; it may be constant or intermittent; it may end abruptly or slowly disappear—but always it is recognizable as fever. Therefore, it seems proper that we should speak of it as the febrile reaction—as something characteristic of the body and not of the disease, and it is from this point of view that I shall consider it. The significance of this reaction I shall discuss later after reviewing the facts concerning the phenomena which are peculiar to it and the upheaval in the whole economy of the body which accompanies it. We shall be particularly interested in comparing it with other reactions, for it is evident to the most casual observer that nearly everything that affects the body at all is responded

*A lecture delivered before the Harvey Society at the New York Academy of Medicine, Nov. 7, 1908.

1. Kraus: von Noorden's Metabolism and Practical Medicine, 1907, ii.

to by some sort of reaction, and that most of these are processes which have been evolved in order to maintain the life and health of the individual. For example, the swallowing of food is followed by the most complicated reactions—muscular movements comminute it, ferments are secreted to digest it, changes in the whole metabolism follow its absorption, and so on. Exposure to heat or cold, hunger or thirst brings into play protective reactions which regulate the body temperature or cut off the lavish expenditure of foodstuff and water still stored in the body so as to protect and prolong life as far as possible. Indeed, it would be difficult to produce such a state of repose that none of these responses would be in progress.

TEMPERATURE REGULATION.

Perhaps the most striking characteristic of fever is the elevation of the body temperature above the normal. The fact that in certain classes of animals the temperature of the body is maintained nearly at a fixed level is in itself a matter to arouse our wonder and interest, and the reason for this regulation of the temperature above that of the surrounding atmosphere (for even in the tropics the average temperature is far below that of the body), and for the constancy of its level would afford much material for discussion. With the exception of mammals and birds, all animals seem to be devoid of any such mechanism and are in consequence poikilothermic.[2] The temperature of their bodies, like that of inanimate substances, quickly adapts itself to that of the surroundings, and heat produced in the course of their metabolic processes is at once dissipated, the more rapidly the smaller the animal on account of its relatively greater radiating surface. In mammals and birds, however, there are special arrangements for preventing such loss of heat, or under other circumstances of facilitating it. Thus the development of the sweat glands in some animals affords them an especially effective method of cooling off the body, while the too great dissipation of heat is prevented in others by the thick layer of subcutaneous fat or the covering of hair or feathers. Man alone finds it necessary to resort to artificial modifications of the temperature of the air and to artificial protection in the form of clothing. It may well be a matter of speculation as to whether, after all, it was not this need of artificial heat regulation which brought about our suddenly acquired knowledge of good and evil rather than the reverse, as is so generally conceded.

Different animals have, of course, different standards of temperature and even for one species there are slight individual variations; nor is

2. Cf. Soetbeer: Arch. f. exper. Path. und Pharmakol., 1898, xl, 53.

the temperature of various parts of the body the same, largely because certain portions are more protected from loss of heat than others, but partly also because, as it seems, heat is more abundantly produced in certain organs than in others. This point may be discussed more advantageously later, but here it may be said that this inequality in local heat production is continuously compensated by the rapid heating of the blood which comes into such close contact with these tissues and then hurries away to warm others.

Although the variations are relatively slight, even warm-blooded animals are subject to changes of a periodic character in their temperature. This is particularly noticeable in birds, in which there is a considerable fall of temperature during the night. I have observed that in normal crows the curve of the temperature, when taken every three hours, shows a regular daily variation of 3 F. or more, the minimum temperature of 104.5 F. being recorded at midnight or at 3 a. m., while the maximum of 108 F. is reached at 3 o'clock in the afternoon.[3] To a certain extent, then, the crow must be regarded as poikilothermic. But even in human beings a similar periodic fluctuation of not more than 1.5 C. is observed and has been recorded in the form of curves by Jürgensen,[4] Benedict and Snell[5] and others. In these curves, as in the case of birds, the lowest temperature occurs in the early morning hours, while the maximum is reached in the afternoon. In addition to the effects of bodily activity of all sorts during the day, it seems possible that there may be causes of a more fundamental character, perhaps even a rhythmicity in the regulation of the temperature, which maintains this uniform curve.

That the temperature of the body is not kept at a perfectly constant level is shown further in the temporary alterations which can result from outward influences and the exercise of bodily functions in the normal individual. Slight elevation of the temperature may follow the taking and digestion of food, and muscular work, if violent enough, may result in a distinct rise in temperature. Ordinarily, however, in freely moving normal animals, such changes are insignificant and compensated at once by the regulating mechanism, and if we observe a marked elevation of temperature in the course of violent muscular activity, it is probably because the normal compensatory dissipation of heat can not take place rapidly enough to keep the body cool. Interest-

3. MacCallum (W. G.): Jour. Exper. Med., 1898, iii, 119.

4. Jürgensen: Die Körperwarme des gesunden Menschen, Leipsic, 1873.

5. Benedict and Snell: Arch. f. d. ges. Physiol., 1902, xc, 33; Am. Jour. Physiol., 1904, xi, 45.

ing examples of this are found in tetanus and the status epilepticus, in which very high temperatures are sometimes observed. I had the opportunity recently of following the temperature in a dog in which after parathyroidectomy the most violent tetany developed with intense spasmodic muscular contractions affecting the whole body. The temperature, which had been 39 C., reached 43.2 C. during this attack, in spite of the fact that the respiration had become extremely rapid (300 to the minute). The administration of calcium acetate stopped the convulsions in a few minutes, and within half an hour the temperature dropped to 38.9 C.

Exposure to excessive heat or cold does not, as a rule, alter the temperature of the normal animal unless the exposure is so protracted and the difference in temperature so great that the mechanism of heat regulation finally becomes inadequate. At a certain limit the control is overpowered and the animal's temperature rises or sinks, as the case may be.

These exceptions to the normal maintenance of a practically constant body temperature, unimportant and transient as they are for the greater part, I have mentioned in order to emphasize the wonderful efficacy of the mechanism of heat regulation. A few words will recall to mind the general character of this mechanism which has at its disposal means for the generation of heat as well as contrivances for the rapid dissipation of the heat produced or for its retention and husbanding within the body. The control of these matters has been clearly shown to reside in the brain, for the severance of nervous connection with the higher parts of the cerebrospinal system leaves the body in the condition of a poikilothermic animal. Whether this is due, as Tigerstedt[6] tends to believe, to the bathing of the brain with blood too hot or too cold or to the transmission of sensations of heat or cold by the nerves, it is difficult to say with certainty.[7] Nor are we satisfactorily informed as to the precise portion of the brain which is concerned in this process of heat regulation, although the discovery of many so-called thermo-regulatory centers has been reported. That one found by Aronsohn and Sachs[8] in the anterior medial portion of the corpus striatum has been most generally accepted, and many investigators have confirmed their statement that the puncture of this area will cause an elevation of temperature which

6. Tigerstedt: Nagel's Handbuch der Physiologie des Menschen, 1906, i, 604.

7. Of great interest in this connection would be the accurate study of heat regulation in patients suffering from syringomyelia in whom all appreciation of heat and cold is lost. Except for the existence of disturbances of the vasomotors of the skin and the sweat secretion, I can find no satisfactory evidence on this point.

8. Aronsohn and Sachs: Arch. f. d. ges. Physiol., 1886, xxxvii, 232.

lasts several days. This sort of hyperthermy has been studied a great deal in connection with fever, and we shall refer to it frequently.

The generation of heat can be effected by the nervous system in the musculature either by the production of actual movements, including such as are evident in shivering, or by the heightening of the muscle tonus. Whether the brain by sending out impulses of any sort to the muscles or to the other tissues can directly accelerate or intensify the chemical processes which lead to the production of heat is still questionable.

The regulation of the dissipation of heat, on the other hand, is very directly controlled by the nervous system, and the mechanism employed is adjusted with great delicacy. Thus radiation and conduction of heat from the surface of the skin depends on the caliber of the cutaneous blood vessels, which can be changed within very wide limits by the vasomotor nerves; in order to keep the body from becoming too warm, whether from excessive production of heat or from the high temperature of the surrounding medium, the skin is flushed with blood, while exposure to cold is quickly followed by such contraction of those vessels that the body surface becomes very pale and the warm blood is restricted as much as possible to the interior and protected from cooling. Even more effective is the secretion of sweat, the evaporation of which keeps the body cool even when exposed to very high temperatures. In all animals, but especially in those which possess no sweat glands, a similar result is attained by the exhalation and evaporation of water from the lungs, and it is well known that in such animals as the dog this is an extremely important method of eliminating heat, the evaporation being greatly increased by acceleration of the respiration. If, as in the experiments of H. Winternitz,[9] the mechanism for the dissipation of heat can be incapacitated by immersing the person in a hot bath at a temperature above the normal body temperature, a curious change occurs in the respiration. Apparently there is no mechanism in the human being to respond to such circumstances by accelerating the respiration, but it becomes greatly increased in volume, possibly in the attempt to compensate for the usual cooling effect of sweating. In dogs so immersed, on the other hand, the rate of respiration increases from about 15 to 300 or more, for the dog still has his normal method of cooling himself.

In such experiments the body temperature and heat production as measured by the chemical changes are greatly elevated and may here be regarded as escaping from the control of the regulating mechanism. On the other hand, if the animal is exposed to cold, as long as its heat-regulating mechanism retains its control and the body temperature re-

9. Winternitz (H.): Klin. Jahrb., 1900, vii, 299.

mains constant, the heat production as measured by the chemical changes is also increased, but sinks when the regulation is no longer maintained and the temperature falls.[10]

HEAT PRODUCTION AND LOSS IN FEVER.

If we now turn our attention to the condition of the temperature, heat production, and loss, in fever, we find that so much light has been shed on the subject in the past few years that we may speak of certain questions with some degree of security, although there remain many points which are still obscure.

It is evident that there are several possible ways in which the temperature of the body may be elevated. The heat production may increase while the heat loss remains constant, or, the heat production remaining constant, the heat loss may be diminished, or both may be elevated but not proportionately. Any disproportion, however slight, between the two which leaves a positive balance of heat will in time bring about an elevation of the body temperature. In this sense we are reminded of the wonderful symmetry of action of the two sides of the heart. The slightest continued disproportion between the output of the two ventricles such that the left ventricle ejects less than the right will in a short time lead to the enormous overdistention of the pulmonary vessels and edema of the lungs. It is plain, therefore, that a great increase in the production of heat is by no means unconditionally necessary for the elevation of the body temperature, and we can readily understand that the continued accumulation of slight excesses may quite rapidly lead to a very striking pyrexia.

Traube attempted to explain fever on the basis of the second alternative mentioned—temperature elevation from excessive retention of heat alone, and supported his theory ingeniously, but it needed only the determination of any increased heat production in cases of fever to shatter this theory. And this proof has been brought by many workers, chiefly by means of a study of the respiratory gaseous exchanges, which showed that oxidation and consequent heat production is increased, but also by the direct measurement of the heat produced by an animal during fever, a measurement which can be carried out by the aid of a suitable calorimeter (direct calorimetry).

It is important to observe that the more recent writers on this subject estimate the increase in the heat production during fever at a much lower figure than did the earlier observers (Senator, Finkler, Colasanti, Lilienfeld and

10. Pflüger: Arch. f. d. ges Physiol., 1878, xviii, 324. Rubner: Sitzungsb. d. Akad. d. Wissensch. zu München, 1885, 458.

others), who often found an increase of 75 per cent. or even more. With Kraus[11] there began a series of more accurate investigations, in which stress was laid on the importance of keeping the animal under observation in a state of muscular repose, since he recognized that the earlier work was untrustworthy on account of the great variations produced by muscular contractions, shivering, etc. After eliminating these sources of error, he found the febrile increase in heat production to be represented by an increase in oxidation of 20 per cent. at the utmost. Löwy[12] also found the increase in combustion relatively slight, sometimes sinking within the limits of normal and at the highest rising to 51.8 per cent.

Nebelthau,[13] recognizing the inaccuracy of this indirect method of estimating the heat production when applied for short periods, studied the heat production and loss in febrile rabbits by direct measurement in a calorimeter, the observations being made to extend over a long period. He, too, found a distinct increase in the output of heat, but thought it still conceivable that fever might arise from the coexistence of a constant heat production and diminished heat loss.

Krehl and Matthes[14] found an increase in heat production of 14 to 60 per cent. in the height of certain fevers, while Staehelin[15] in his febrile dog observed at first a diminished heat production, although later in the height of the fever the normal was exceeded by 45 to 47 per cent. May[16] in febrile rabbits similarly found a normal heat production on the first day of the fever, but a rise of 5 to 28 per cent. on the second day.

All these authors agree, therefore, that in fever there is a distinct increase in the heat production. When they speak of an increase of 25 to 50 per cent. in the heat production as compared with the normal it seems at first sight an enormous change. The true significance of this statement is not clear, however, until we examine the heat production under some other conditions, and a hint of the relative importance of the influence of these other conditions is given by the refusal of the recent workers to accept the results of their predecessors because they had not carefully attended to the exclusion of the effects of chance muscular movements during the observations. Speck[17] even goes so far as to assert that there is no increased heat production in fever, that even the modern figures are a delusion based on the overaction of the respiratory muscles, the intensification of the heart beat, etc.

The amount of heat produced in the body on the ingestion and absorption of a full meal is very greatly increased over that produced by the same person when at rest and with an empty stomach. Many earlier workers have demonstrated this, and Staehelin,[18] in his recent careful study, has shown very clearly the effect of various forms of food, the

11. Kraus: Ztschr. f. klin. Med., 1890, xviii, 91.
12. Löwy: Virchow's Arch. f. path. Anat., 1891, cxxvi, 218.
13. Nebelthau: Ztschr. f. Biol., 1894, xxxi, 293; Arch. f. exper. Path., xlvi.
14. Krehl and Matthes: Arch. f. exper. Path., 1897, xxxviii, 284.
15. Staehelin: Arch. f. Hyg., 1904, L, 77.
16. May: Ztschr. f. Biol., 1893, xxx, 51.
17. Speck: Physiologie des Menschlichen Athmens, Deutsch. Arch. f. klin. Med., 1892, xlv, 461.
18. Staehelin: Ztschr. f. klin. Med., 1908, lxvi, 201.

increased energy production being greatest after a meal composed of carbohydrate and proteid. Such an increase in heat production may surpass by a great deal that observed in fever, but there need be no rise in temperature. With muscular work the increased heat production is enormously greater. In contrast with the febrile patient at rest, in whom, as we have seen, heat production reaches a moderate excess, the normal man, in the course of muscular labor, produces an amount of heat often several hundred per cent. in excess of that developed while he is at rest —and still there need be no elevation of his body temperature. He differs from the febrile patient in the extraordinarily rapid discharge of heat by all the means at his disposal.

Although it is obvious from the direct calorimetric estimations mentioned that the heat loss is increased during fever as well as the heat production one must gather, from the knowledge of the normal methods of heat regulation during great elevations of the heat production, that in fever the dissipation of heat is relatively restricted, and that, even though the body has not at its disposal the enormous quantity of heat produced by the well-fed and working man, the metabolism is somewhat accelerated and some of the excessive heat is retained. This is sufficiently clear, although I can not find perfectly precise measurements of the amount of heat produced during a certain period contrasted with the amount lost in the same period in order to show concretely the direct cause of the elevation of temperature.

Liebermeister,[19] as is well known, entertained the view that the regulating mechanism is in fever peculiarly altered to react for a different standard of body temperature. As he expresses it, the regulating mechanism is tuned up to a higher pitch so that it begins to allow of the escape of heat only at a higher level, exactly as we might screw up the thermoregulator of a thermostat so that its temperature would stand at 40 instead of 35. There is something very attractive about this idea, but it must be said that the experiments which might establish it as a fact have not been carried out satisfactorily.[20] In general it is known that

19. Liebermeister: Pathologie der Fieber, 1875.

*Efforts have been made by Stern, Filehne and others to show that there is some such constancy in the activities of the heat regulating mechanism, but Krehl points out very justly as it seems the fact that there is rather a weakening of the control so that febrile patients are more subject to external influences than normal persons—they are more easily cooled in a cold bath and more subject to the effects of antipyretics. Of course, the abnormal condition of the cutaneous vessels and other instruments of the regulatory mechanism must be remembered, but the very inconstancy of the body temperature during fever seems to him enough to indicate that here we are not dealing with an adequate regulating mechanism which is merely tuned to a higher pitch, but rather with one which to a certain extent has lost its control.

muscular effort during fever may drive the temperature up—that the taking of food may elevate the temperature, and that even after convalescence has begun the temperature regulation of a febrile patient is very labile and easily disturbed. But we do not know precisely whether the output of heat produced by muscular work during fever would be regulated at this higher standard in a way resembling that in the normal. If Liebermeister's theory is to hold, the heat produced from muscular work should be dissipated after the requisite amount to maintain the heightened body temperature has been accounted for, in the same way as in the normal.

Much interest is attached to the variations in heat production and loss, and the consequent temperature in the various stages of fever. It seems probable that this must vary in different types of fever, for the characters of these stages differ so much, but it is certain that in the initial stage, especially in those cases in which fever is ushered in by the appearance of a chill, every mechanism is set to work by the body to limit, as far as possible, the escape of heat and by increasing at the same time the heat production to elevate the temperature as rapidly as possible. The skin becomes livid and blue and cold as the result of the energetic contraction of the cutaneous vessels; the very important methods of heat loss, radiation and conduction, are thereby restricted to the maximum degree. Evaporation from the skin and from the lungs is also decreased, although in some cases that from the lungs has been observed to be heightened. Further, the patient, from the very sensation of cold produced by these changes, draws his body into the smallest compass and covers himself thickly with clothes. On the other hand, heat production is greatly increased, and especially so by the increased tension of the muscles, the shivering and even by the goose flesh. Liebermeister found an increase of 21 to 24 per cent. in the heat production in the hot stage of a malarial attack, in the chill 147 per cent. increase. Naturally the muscular contractions are chiefly responsible for this high figure. Krehl and Matthes[20] find that in this stage both heat production and heat loss fluctuate a great deal, but that they diverge from one another far more than in the normal.

During the fastigium or height of the fever the disproportion between heat production and heat loss is less striking. Conduction and radiation of heat from the skin and evaporation approach the condition found in the normal person on the same diet[21] and in the same surroundings, but this in itself is abnormal, for in a healthy person with

20. Krehl and Matthes: Arch. f. exper. Path., 1897, xxviii, 284.
21. Krehl: Ztschr. f. allg. Physiol. (Verworn's), 1902, i, 29.

such an elevated heat production these regulating mechanisms would be greatly stimulated.

The blood supply to the skin in the height of fever undergoes remarkable fluctuations, as Senator[22] pointed out; the dilatation and contraction of the vessels may vary from hour to hour and even from one part of the skin surface to another, and consequently it seems probable that if we could determine the heat loss from the skin for very short periods we would obtain a curve showing very marked irregularities. In this stage, then, we have an irregular and moderate increase in the heat production associated with an irregular increase in the heat loss. However much the heat production may increase, the heat loss keeps a place somewhere behind it, and there is no parallelism between the temperature and the heat production or between temperature and the amount of oxidation going on. Krehl and Matthes point out the fact that the special cause of the fever does not necessarily govern the intensity of the heat production, over which the nutritive condition of the patient and the individual type of reaction have a great influence. The young strong patient tends to show a higher heat production than does the aged, weak one, and it is a commonly appreciated fact that the lack of an intense febrile reaction, like the absence of adequate leucocytosis, is often an index of the low powers of resistance of the patient. When a patient is overcome by the intensity of the infection, it is also usual to observe a fall of body temperature to a subnormal level.

In the last stage of fever, that of defervescence, there is a gradual or sudden strengthening of the mechanical dissipation of heat and at the same time a decrease in the heat production. One receives the impression that the mechanism of heat elimination, having been held in leash by the regulating nervous system, is now set free when the poisoning is overcome and the saving of heat no longer necessary. Especially in the critical forms of defervescence is this outbreak of heat dissipation seen to advantage, merely because there the phenomena are concentrated into a short period of time.

TOPOGRAPHY AND MECHANISM OF FEBRILE HEAT PRODUCTION.

Since I wish to discuss in some detail the changes in metabolism which underlie these disturbances of the heat economy of the body, the limits of this lecture will not allow me to enter on a consideration of the topography of heat production further than to say that the muscles are commonly regarded as the great source of heat, although, of course, every tissue is concerned to some extent in its development. In fever

22. Senator: Untersuchungen über den Fieberhaften Process, 1873.

there are, as we shall learn, certain special reasons for thinking that heat production is brought about chiefly in the muscles. There are, however, those who disagree with this assumption and believe that the liver is even more prominent in this connection. Hirsch and Rolly[23] find that after the influence of the muscles is destroyed by curare, it is still possible to produce hyperthermy by heat puncture, and, since this is not successful in glycogen-free animals, they ascribe the production of heat to the combustion of carbohydrates in the liver, and by thermoelectric methods show that it is only after the temperature rises in the liver that it does so in the muscles. Hirsch and Müller[24] apply the same thermometric and thermoelectric methods to the mapping out of the heat production in the body, and find in fever that the liver is far warmer than the muscles, and that even the subcutaneous tissues have a higher temperature. They regard the low temperature of the muscles as notable, and hold that Heidenhain's view that the muscles are warmer than the aortic blood is thus disproved. The methods employed in these researches seem not entirely above criticism, for we have again a conclusion as to heat production based on the temperature of an organ, and, in my judgment, we must still defer our ultimate conclusion as to the relative importance of the muscles until further work is brought out.

Nor can I consider at length the interesting discussion as to the claims of the theories of the neurogenic and toxogenic nature of fever. The precise character of the nervous mechanism which presides over the heat economy of the body is far from being well understood, but I have already mentioned the fact that there are certain localities in the brain, irritation or injury of which causes hyperthermy, and have drawn especial attention to that so-called heat center which was discovered by Aronsohn and Sachs in the anterior medial portion of the corpus striatum. The character of its action is, however, not understood; we are far from possessing definite proof of the existence of any special nerves which preside over the production of heat, and it is at this point that the neurogenic theory of fever is attacked. Hirsch, Müller and Rolly[25] put forward the idea that it is not from the action of the nervous system that the febrile intensification of metabolism arises, but rather from the introduction of poisonous substances which directly injure the cells. While the neurogenic chemical heat regulation occurs in the muscles with the increased burning of carbohydrate, the increased burning

23. Hirsch and Rolly: Deutsch. Arch. f. klin. Med., 1903, lxxv, 307.
24. Hirsch and Müller: Deutsch. Arch. f. klin. Med., 1903, lxxv, 286.
25. Hirsch, Müller and Rolly: Deutsch. Arch. f. klin. Med., 1903, lxxv, 265.

in fever is probably universal and affects especially the proteids, the part played by each organ depending on the intensity of its specific function in metabolism. Fever is thus a specific reaction against injurious materials which affect the tissues. Krehl and Soetbeer[26] find that in cold-blooded animals, such as the frog, infection results in a marked heat production and dissipation; and, inasmuch as these animals have no nervous mechanism controlling heat regulation, they see in this result a proof of the toxogenic theory of fever.

It would seem perfectly possible to control the part played by the nervous system in fever by a variety of experiments. No one doubts the dependence on the nervous system of the mechanism governing the dissipation of heat, and the question is rather as to the relation of the heat production to the superior nerve elements. Of course, it is plain that by causing muscular contraction or increasing muscular tone the motor nerves can increase heat production, and one might be inclined to say that in all probability this is the way in which the heat production is stimulated in all cases. But it is frequently observed that when the spinal cord high in the neck is severed there occurs a febrile rise in temperature with increased heat production,[27] although often it is the reverse, a gradual sinking of temperature. Section of the medulla near the pons causes a rise in temperature, and the injury of the corpus striatum spoken of above very regularly brings this about. Analysis of such effects shows that the elevation of temperature is not due solely to limitation of heat dissipation, for Schultze[28] finds that animals with heat puncture react to outward changes in temperature precisely as do normal animals. There is, on the contrary, an actual increase in the production of heat, even though the animals remain perfectly quiet, and, although there has been some disagreement as to the actual source of the heat, in these cases it seems probable that we must accept the results of Senator and Richter,[29] who find that there is not merely an increased combustion of carbohydrates, but that proteid metabolism is also increased. In no essential particular, then, does this hyperthermy differ from that of fever.

Despite all this evidence that a somewhat peculiar febrile reaction can be produced by injury of the brain and despite the perfectly certain

26. Krehl and Soetbeer: Arch. f. exper. Path. u Pharmakol., 1898, xl, 275.
27. Krehl: Verhandl. d. Cong. f. inn. Med., Wiesbaden, 1898, xvi, 229.
28. Schultze: Arch. f. exper. Path., 1900, xliii, 193.
29. Senator and Richter: Ztschr. f. klin. Med., 1904, liv, 16.

and generally accepted fact of the nervous control of the heat-dissipating apparatus, I feel that there is much to be said for the view that the circulating poisons affect directly all the cells of the body, and that the latter in their quality of living protoplasmic creatures react with an increased metabolism. It appeals to me as a reaction quite analogous to that in which leucocytes are produced in enormous numbers in the far-off bone marrow when they are needed in the pneumonic lung, and is no more easily explicable than this.

METABOLISM IN FEVER.

Having discussed the general subject of heat regulation in connection with fever, in some of its aspects, we may now turn to the consideration in somewhat greater detail of the chemical processes which underlie the production of heat. It may be said in general that these processes, in so far as they are connected with heat production, consist chiefly in the combination of oxygen with carbon and with hydrogen with the formation of carbon dioxid and water. That this outcome may be interrupted by the formation of intermediate products detracts in no way from the truth of this statement, and if only sufficient time be devoted to observation the final results are the same. That there are other oxidations going on is, of course, true, but their rôle in comparison with those mentioned is almost negligible. Further, the amount of heat produced in the various decompositions and syntheses is very slight, and we shall not go far astray in restricting our attention to the oxidation.

Something has already been said concerning these processes in discussing the production of heat in so far as the amount of heat produced in fever was compared with that produced in other conditions. Now, however, it is important that we should be able to compare more accurately the figures which result from the estimations of oxygen in varying conditions, and at the risk of becoming tedious I shall quote the statements of various authors as to the total oxidation products in various stages of hunger and nutrition, in muscular work, in exposure to heat and to cold and finally in fever. Naturally these results may vary widely because of the size and characteristics of the individual observed and because of difference in the character of the nutrition, but they will doubtless diverge so far from the normal that there can be no question as to the effects of the conditions which they are meant to illustrate. For the sake of convenience, they may be set down in the form of a table.

TABLE SHOWING STATEMENTS OF VARIOUS AUTHORS AS TO OXIDATION PRODUCTS IN VARIOUS CONDITIONS.

Subject.	Condition.	CO_2 Output. c.c. per Min.	CO_2 Output. gm. per Hour.	Oxygen Absorption. c.c. per Min.	Oxygen Absorption. gm. per Hour.	Author.
Healthy Man—						
In bed, fasting.	Especially quiet.	.....	21.4	.....	.....	Johannson[30]
Ordinarily quiet	.....	.....	28.1	.....	.....	
Healthy Man—						
Fasting	.....	.....	36.5	.....	.....	
During and after meal	.....	.....	41.5—49	.....	.....	
Sleep	.....	.....	30	.....	.....	
After five days' hunger. At rest or reading	.....	.....	24—29	.....	.....	Johannson[31]
During and after a walk	.....	.....	30	.....	.....	
Sleep	.....	.....	18	.....	.....	
Healthy Man—						
Exposed to cold and heat.						
Surrounding temperature, 4.4°C	.....		35.16	.....	.....	Voit[32]
Surrounding temperature, 15.2°C	.....		26.33	.....	.....	
Surrounding temperature, 30°C	.....		28.5	.....	.....	
Healthy Man—						
Rest	.....	.....	27—37	.....	.....	
Walking	.....	.....	49—67 (increase 13—45)	.....	.....	
Climbing	.....	.....	86—131 (increase 50—104)	.....	.....	
Healthy Man 67.2 kg.—						
1. Complete repose. Fasting	.....	.....	19.86	.....	17.45	Staehelin[33]
2. Complete repose. Proteid meal, 75 gm. proteid	.....	.....	23.50	.....	22.54	
3. Complete repose. Fat meal, 7 gm. proteid, 77.4 fat, 30 carbohydrate	.....	.....	22.65	.....	21.88	
4. Complete repose. Carbohydrate meal, 32 gm. proteid and carbohydrate, 189 fat	.....	.....	24.08	.....	21.41	Staehelin[34]
5. Complete repose. Proteid and carbohydrate, 90 gm. proteid, 34 gm. fat, 113 gm. carbohydrate	.....	.....	25.80	.....	23.61	
Healthy Man, 48 kg.—						
At rest. Temp. 36.2	.....	133.8	15.86	172.9	14.38	Winternitz[35]
After 35 min. in bath at 40-41 C. Temp. of pt. 38 C	.....	316.2	37.50	363.6	31.18	

30. Johannson: Skand. Arch. f. Physiol., 1897, vii, 172.
31. Johannson: Skand. Arch. f. Physiol., 1898, viii, 108.
32. Voit: Ztschr. f. Biol., 1877, xiv, 79.
33. Staehelin: Ztschr. f. klin. Med., 1908, lxvi, 201.
34. Staehelin: Ztschr. f. klin. Med., 1908, lxvi, 201.
35. Winternitz (H.): Klin. Jahrb., 1900, vii, 1.

Subject.	Condition.	CO_2 Output. c.c. per Min.	CO_2 Output. gm. per Hour.	Oxygen Absorption. c.c. per Min.	Oxygen Absorption. gm. per Hour.	Author.
Woman, 61 kg.—						
Erysipelas.	Temp. 40 C.	303.91	36.02	321.41	27.57	Kraus[36]
Fever-free one month later		224.68	25.64	245.18	21.3	
Man, 48.5 kg.—						
Typhoid, 2nd week.	Temp. 39-40.8.	284.12	33.69	350.4	30.02	
Man, 48.5 kg.—						
Pneumonia.	Temp. 38.9-40.5	234.9	27.85	25.56	21.91	
Man, 58 kg.—						
Pleuritis.	Temp. 39.5	254.78	30.21	315.1	27.02	Löwy[37]
Man—						
Typhoid.	Temp. 39.5	263.99	31.30	398.32	34.16	
Man, 50 kg.—						
Typhoid.	Temp. 39.5	205.79	24.40	291.72	25.02	
Man, 50.5 kg.—						
Tuberculosis.	Temp. normal	206.29	24.43	255.95	21.95	
Tuberculin injection.	Temp. 40.2	280.96	33.12	316.25	27.15	
Woman, 61.4 kg.—						
Suspected tuberculosis.	Temp. 36-37	289.51	34.22	381.41	32.71	Kraus and Chvostek[38]
Tuberculin injection.	Temp. 39.2	310.84	36.86	417.20	35.78	
Woman, 46 kg.—						
Pulmonary tuberculosis.	Temp. 37.9	184.15	21.83	268.07	22.99	
Tuberculin injection.	Temp. 40.2	258.97	30.71	399.17	34.32	

This table suffices to show that in fever in man the oxidation is usually but not necessarily increased, but that the increase is not very great. Kraus estimates it is not exceeding 20 per cent. at the highest, while in some cases it is not elevated at all. And Löwy, Riethus and others concur with him in this opinion, believing that the higher percentages given by the earlier workers (Senator 75 per cent.) were probably dependent on the muscular unrest which prevailed during their observations. Similar results have been obtained in the case of animals in which fever has been experimentally produced, and I need only refer here to the careful studies of May[39] and Staehelin.[40]

May gives the result in one of his hungering rabbits in which he produced fever by inoculation with the bacillus of swine erysipelas as follows:

Rabbit E.	CO_2 Output.	Oxygen Absorption.	Resp. Quotient.
Before infection	48.756	46.861	0.7567
After infection and during fever	53.035	50.700	0.6953

Here we have an increase in the carbon dioxid of only a little more than 8 per cent., and Staehelin in observing the dog infected with surra found the following changes in the carbon dioxid output:

36. Kraus: Deutsch. Ztschr. f. klin. Med., 1890, xviii, 160.
37. Löwy: Virchow's Arch. f. path. Anat., 1891, cxxvi, 218.
38. Kraus and Chvostek: Wien. klin. Wchnschr., 1891, 607.
39. May: Ztschr. f. Biol., 1893, xxx, 1.
40. Staehelin: Arch. f. Hyg., 1904, l, 77.

	Carbon Dioxid, Output Per Day. (Average of Several Days).
Before infection	178.6
After infection—First period. Temp. 37.9-39.4	169.85
Second period. Temp. 39.5-40.1	206.75
Third period. Temp. (?)	229.0
Fourth period. Temp. 38.5-40.4	195.5

The maximum increase of carbon dioxid in this case is 28 per cent.

It is obvious that the value of such estimations of the total oxidation in fever lies in the fact that we can thus compare roughly the extent of the oxidation in that condition with that observed in a normal person, or in a person doing muscular work, and can judge as to whether the metabolic changes are in gross greater or less than in those persons. We may even compute, if we know the total nitrogen output, the proportion of this total oxidation which pertains to the burning of nitrogenous materials and that which results from the combustion of the nitrogen-free substances; but, unless we know more than this, we can gain no very accurate idea as to the more intimate nature of the processes which go on in fever as contrasted with those in a healthy person. It is known, for example, that in the healthy person, as long as there is a sufficient supply of energy-producing food, the tissues themselves are not attacked; it is known, further, that the oxidation in the normal person is very much modified by the character of the food, and, still further, that in muscular work in the normal individual the oxidation associated with the supply of energy for the work does not affect even the circulating proteins, so long as there is abundant supply of non-nitrogenous materials. These things are, however, by no means to be assumed as true in the case of the febrile person. We must, therefore, in order to determine the exact nature of the processes of oxidation in such a person, even more than in the normal, make such studies as will give us evidence of the exact amount of protein, of carbohydrate and of fat in the food; we must know the amount of water taken into the body and, if possible, the amount of oxygen absorbed. We must then know the output of these various substances, preferably in health and in fever in the same individual, and this information must include at least the amount of nitrogen excreted in the urine and feces, and the amount of carbon in the urine, feces and respiration as well as the amount of water excreted by these channels. We can then, and then only, determine the balance of nitrogen, carbon and water; and in order to estimate with any accuracy the suspected changes in the tissues such information as to the balance seems necessary. Even then the methods which have been mentioned for the appraising of the amounts of the non-nitrogenous substances oxidized are perhaps not absolutely to be relied on, for unless the animal is

starved until it can be regarded as glycogen-free—always a doubtful assumption—we must depend on the idea that after the amount of carbon dioxid corresponding to the nitrogen excretion is deducted the remainder is to be applied, first, to accounting for the oxidation of carbohydrate and only after that the oxidation of the fat. Further, the existence of the intermediate products of oxidation can not be suspected unless we know the respiratory quotient; that is, the relation of the output of carbon dioxid to the absorption of oxygen.

The exact estimation of the nitrogen balance seems to be of especial importance in the study of the protein changes in fever which are so prominent. In the literature of the subject, however, I can find no such studies of fever in man; nearly all—I may say all—are fragmentary in the sense that the character of the food is not recorded or that the estimations of excreta are not sufficiently complete to enable one to do more than infer from comparison with approximately similar estimations, in the normal, the nature and extent of the change. Naturally only divergences of considerable extent from the average normal will be recognized in this way. The recent researches of Staehlin on the metabolism of nonfebrile tuberculous patients give, however, a very good model for such work.

Nevertheless, the principles involved are rendered clear in the papers already mentioned of May and Staehelin.

May starved his rabbits until a uniform nitrogen output was established and then inoculated them with the bacillus of swine erysipelas and was able to draw up such tables as the following, in which, since the rabbit received no food, he could accurately assign the oxidation products to the body tissues from which they sprang:

Temperature of Animal.	Nitrogen of Urine.	Carbon		
		Respiratory Carbon.	From Proteins.	From Non-Nitrogenous Materials.
39.5.....	1.30	.....	.....	.....
39.2.....	1.45	.....	.....	.....
39.5.....	1.79	13.22	5.796	8.848
39.7-41.2.....	1.81	13.10	5.864	8.675
40.8-40.7.....	2.45	14.53	7.938	8.545
34.7-32.5.....	0.103	12.337	....	..... Collapse

Staehelin fed his dog but estimated precisely the constituents of the food and the consequent nitrogen and carbon balance in the excreta. From this, since the deficit of nitrogen and carbon showed that there was constant tissue destruction, he could feel sure that the increased output of carbon was derived from body protein and body fat and could estimate the proportion in which they were oxidized. His tables[41] show very plainly that there is not only a rapidly increasing protein destruction during the fever but that there is also an increasing oxidation of body fat, which is far too great to be ascribed to inanition. To this relation of the fat it will be necessary to return. Staehelin summarizes the total body destruction of the animal in this experiment as follows:

41. Staehelin's tables are too long to reproduce here, but they have been copied by Kraus in von Noorden's Metabolism and Practical Medicine, Volume II, where they are perhaps more accessible than in the original paper.[40]

	Protein Destruction.	Fat Destruction.
Preliminary period	8	51
Inoculation and prodromal	17	73
First period of fever	29	49
Second period of fever	110	204
Third period of fever	47	79
Final period	143	175

The value of the respiratory quotient which gives us a clue as to the qualitative character of the oxidation processes does not seem to have been as great in the case of fever as might have been expected, for there is still much dispute as to its amount in that condition. The earlier authors found, as a rule, that this coefficient was lowered in fever—thus Regnard, Riethus, Finkler and Löwy all report such a diminished respiratory quotient. Senator sums up his results in the following statements:

Even in the most favorable case the increase in the carbon dioxid output is far less than the increase in the urea excretion. In the febrile body there is not (unless perhaps in the earliest hours of the fever) any abnormal accumulation of carbonic acid—rather the reverse. Therefore, in fever the burning of nitrogen-free carbonaceous material (fat) to its end product (carbon dioxid) can not occur to the same extent as the decomposition of protein into urea. On the contrary, there seems to be rather a decrease of fat combustion than an increase, and the fevered animal will therefore become relatively richer in fat than a non-febrile animal in the same condition of nutrition. This probably explains the fatty degeneration which occurs in the tissues in febrile diseases.

Kraus, in 1891, found that no direct relation existed between the extent of oxidation and the degree of pyrexia and concluded that any qualitative alteration of febrile metabolism that might be found was insufficient to influence the respiratory coefficient in a recognizable degree. As a matter of fact, he found the quotient practically unchanged and thought that any changes which might occur were determined by the existing nutritional state, by the bodily condition and by the material available for metabolism. Jaquet has adopted the same view and has shown that a diminution of carbon dioxid elimination in the respired air may depend on a diminished respiratory effort and less complete ventilation of the lung.

Staehelin gives the following figures from his experiments (average in round numbers):

	Respiratory Quotient.
Normal person, fasting	0.82
Normal person, after protein meal	0.78
Normal person, after fat meal	0.75
Normal person, after carbohydrate meal	0.81
Normal person, after mixed protein and carbohydrate	0.79
Pathologic person, carbohydrate meal	0.89
Pathologic person, after protein meal	0.89
Pathologic person, fasting	0.75

On the whole, it seems that the respiratory quotient as such can at best give only a suggestion as to the probable predominance of one material over the others in metabolism, for it is not changed by a meal composed exclusively of protein nor by muscular work.

PROTEINS AND FATS IN FEVER.

This leads to the consideration of the fate of the foodstuffs and body constituents in fever as contrasted with health and we may well begin with the protein substances, since our knowledge of the part they play is much greater than in the case of the rest. Since the work of Vogel[42] and Traube[43] it has been known that in fever the most striking change in the character of the excretion consists in the greatly increased output of nitrogen in the urine. Senator found this in his feverish dogs and the quotation from his work just given shows fairly well his familiarity with the fact. Since these earlier papers every worker on the subject has confirmed this fact.[44] The amount of the excess of nitrogen varies in different cases according to the intensity of the disease and with the cause, but there is no constant parallelism between these things. Especially can it be said that the curve of the nitrogen excretion is not parallel with that of the temperature, for there are many infectious and toxic conditions in which the nitrogen output is greatly increased, but in which there is no fever at all. In the estimation of the amount of this excretion which can be regarded as abnormal, not a few difficulties are met with, as I shall try to make clear.

Speck,[45] in his review of the subject of nutritional and energy metabolism, emphasizes the idea of the existence of two kinds of protein in the body, one the living protein of the cell, which is very resistant to decomposition, while the other, the circulating protein absorbed from the food, is readily oxidized and excreted as urea. When an individual is in brisk muscular action the respiratory interchange is heightened, the excretion of urea is not much increased and the heat production and liberation of mechanical energy is thought to be due to burning of the nitrogen-free elements. It is only when these are lacking that protein is extensively used for such a purpose, and there is no store of really labile nutrition protein for this purpose. The decomposition of the organic

42. Ztschr. f. ration. Med., 1854, new series, iv.

43. Traube: Deutsch. Klin. 1855, xlvi, 511.

44. Leyden and Klemperer reported a loss of 109 gm. of nitrogen equalling 3.2 kilos of muscle tissue in twelve days, and Friedrich Müller in another case determined that there was lost an amount of nitrogen (86.4 gm.) corresponding to 2.5 kilos or 5.5 pounds of muscle tissue in eight days. Frequently, as will be pointed out, this loss is greatest during defervescence.

45. Speck: Ergebn. d. Physiol., 1903, ii, 1.

protein is completely different from that of the unorganized and follows other laws, being inconspicuous in normal conditions, but conspicuous in certain abnormal states, such as insufficient oxygenation, various intoxications and fever. When it does break down it becomes inanimate circulating protein, but its products of decomposition lag behind in the body and are excreted only slowly. Then, however, the urea output is incomparably greater than that appearing after muscular work and is more closely approached by that following the ingestion of excessive amounts of protein. Such disturbances are affections of the metabolism of nutrition rather than that of energy production.

It is evident from this, as I have emphasized before, that in order to obtain any unassailable information as to the character and source of the protein excreted and the amount of its excess, we must study it either in an animal in a state of complete starvation or in an animal reduced to nitrogenous equilibrium in which we know precisely the amount of protein ingested and can estimate the respiratory changes.

That the nitrogenous excretion in fever is increased above the normal and above an amount which could be accounted for by the food is perfectly evident from the results of all experimenters. Senator estimates the amount as about double that found in the normal, but it differs in different cases and tends to sink in the later stages of the fever, always remaining above the normal, however. In those diseases in which there is a sudden or critical fall in temperature there is often an especially intense epicritical excretion of nitrogen after the crisis. This is explained sometimes as due to the retention of nitrogenous excreta in the body until that period, or again as the result of the febrile inhibition of urinary secretion. Another explanation is found in the idea that the exudate of cells produced during the inflammatory process which caused the fever is suddenly absorbed and its nitrogenous portion excreted; but this suggestion is weakened by the fact that the same epicritical rise may occur in inflammatory diseases in which there has been no such accumulation of exudate.

For an exact study of the nitrogenous excretion in fever which satisfies our demand for certainty rather than conviction we may refer to the experiments of May and Staehelin once more. May found that in his rabbit with the advance of fever and without food the nitrogenous output, which by that time must depend on destruction of the tissue proteid, advanced from 1.79 to 2.45 gm. per day, while Staehelin found that the negative nitrogen balance which appeared during the prodromal period of the fever increased gradually until the death of the animal from 0.5 to 4.70 gm. per day. There is no question, then, that in this

instance, in spite of the available food, there was an actual attack on the tissue proteid, and we are led to inquire whether this is always the case or whether possibly, as May maintained, the destruction of tissue protein is due to an insufficient supply of nitrogen-free and nitrogenous substance in the nutriment. The very fact that in hunger the extent of the protein decomposition is so promptly changed by the onset of fever seems almost sufficient to decide this question, but it is put in a clearer light by the experiments of Weber,[46] who studied the changes which he could produce in a sheep which he could render feverish by injection of a toxin extracted from glanders bacilli, by the administration of different amounts of carbohydrate in the food. He found first that, although it took an amount of nourishment which would under normal conditions maintain nitrogenous equilibrium and yield a sufficient amount of available energy, it still lost protein during fever. When, however, he first elevated its protein store by abundant feeding and continued the abundant feeding of protein and carbohydrate he found that even during fever there might be maintained a saving of protein. He was not able to estimate exactly the protective action of the carbohydrate or protein consumption during fever, because of the difficulty in getting the animal to consume enough of it. As F. Müller[47] points out, we can not assume from any such experiment that the protein decomposition in fever is the same in character as that in health, nor can we demonstrate in this way the existence in addition to the ordinary protein destruction, of another form due to the cause of the fever. P. A. Shaffer[48] has in the same way been able to protect the body proteid from consumption in typhoid fever by the administration of a diet rich in carbohydrates.

It is interesting to compare the nitrogenous excretion in forms of hyperthermy not produced by infection with that found in infectious fever. Such, for example, are the hyperthermy following so-called heat puncture and that resulting from overheating. In both of these conditions it is found that there is an excessive excretion of protein as well as an increase in the general oxidation processes. This is particularly striking in the experiments made by immersing persons in a hot bath as carried out by Winternitz, in which he found that the absorption of oxygen and the excretion of carbon dioxid was far in excess of that observed in any infectious fever, and approached more closely the effect seen in violent muscular work. Others, such as Topp,[49] Schleich and

46. Weber: Arch. f. exper. Path., 1901, xlvii, 19.
47. Müller (F.): Leyden's Handbuch der Ernährungstherapie, 1898.
48. Shaffer (Philip A.): Metabolism in Typhoid Fever, Jour. Am. Med. Assn., 1908, li, 974.
49. Topp: Inaug. Diss., Halle, 1893.

Formanek,[50] have shown that the protein output is also greatly increased. On the whole, the result seems to be very similar to that which might be produced not only by muscular work, but exhaustion from such work. It would be a matter of extreme interest to determine in this case whether the protein decomposition is due to the insufficient supply of carbohydrate only, or whether it is actually the result of the heat injury to the muscles. Winternitz's experiments were carried out on fasting persons, and it seems possible that had these persons been supplied with very abundant carbohydrate food the excessive nitrogen excretion might have been spared, as, indeed, was the case in Voit's[51] dog.

We are hardly in a position to determine even from these experiments as they stand to what extent the height in temperature as such brings about an increased protein decomposition, but the general assumption is that it plays a considerable part. It is none the less a fact, supported by very abundant evidence, that when the utmost effect of hyperthermy is taken into consideration there still remains in fever an excessive excretion of nitrogenous material which must be accounted for by direct injurious action on the protein of the agent which causes the fever.

The nature of this injurious process, which is very indefinitely spoken of as a toxic destruction of the cells, must differ widely in different cases, and must in many instances be quite out of proportion to any effect which it produces in the form of fever, for it is well known that there are many infectious and toxic processes associated with extreme destruction of the tissues in which there is no febrile reaction at all. It is, therefore, quite impossible for us to form any estimate from the composition of the excreta as to the extent of the febrile reaction which may have occurred. Nor is it possible in the present state of our knowledge for us to recognize any peculiar type of alteration of the tissue which can be regarded as particularly associated with the discharge of this reaction.

There seems to be at least two distinct types of protein decomposition which may take place in the tissues: first, that in which the protein stored in the tissues is decomposed by the action of the living cell itself, and, second, that which goes regardless of the influence of the cells, and in dead protoplasm as the result of the activity of certain ferments which are commonly spoken of as proteolytic ferments, and which play such an important part in the process of autolysis. It seems quite possible that these ferments or similar ferments may also be concerned in

50. Schleich: Arch. f. exper. Path., 1875, iv, 82.
51. Voit (F.): Sitzungsber d. Gesellsch. f. Morphol. und Physiol., 1895, 120.

the vital activities of the cells, and form the instrument by which they produce the necessary decomposition of protein material, but we are quite certain of their activities in the process of autolysis.

How these processes are affected by the injurious agent in fever is not perfectly clear, but it may well be imagined that by the destruction or injury of cells, more material is furnished for the autolytic decomposition of protein which differs in some degree from the vital destruction of protein. Some light is thrown on this by the recent discovery by Aronsohn and Blumenthal,[52] that there occurs in the course of fever a very greatly increased amount of proteolytic ferment in the muscles, while that in the liver is somewhat diminished.

The biologic significance of this destruction of tissue is by no means clear, but Kraus makes the suggestion that it may prove to be explicable by hypotheses similar to those which Ehrlich adopts in his theories of immunity, and that, in fact, it is probably in some way associated with the development of immunizing or protective substances. This will be referred to later.

When we attempt to assign to a source in the body the protein which we may thus assume to be derived from living tissue, we have very little basis on which to go. Salkowski concluded from the fact that in fever an excessive excretion of potassium accompanies the increased output of nitrogen, that the nitrogen is probably derived chiefly from the muscles, but other than this we have very little information. In view of the fact that the total oxidation is not greatly elevated in fever, it is important to know whether the protein is completely oxidized in the body or whether possibly intermediate products derived from the non-nitrogenous portions of the protein are stored there. This, as is well known, was maintained by Senator, who thought, as we have mentioned before, that the body became during fever richer in fat. Fraenkel, too, finds it easier to explain the excessive excretion of urea on the basis of inadequate oxidation than otherwise, for an analogue is found in such types of intoxication as phosphorus poisoning, in which an excessive amount of urea is excreted and fat at the same time stored up. This brings us to the discussion of the question of fat metabolism in fever, which may be considered parenthetically here, since we know so little about it. It still remains a question as to the degree of oxidation of fat in the course of fever, and, as I have said, the older ideas of Senator begin to be contradicted by such work as that of Staehelin, in which an excessive consumption of the body fat can hardly be ascribed merely to inanition. Most authors writing on this subject assume that the gradual wasting

52. Aronsohn and Blumenthal: Ztschr. f. klin. Med., 1908, lxv, 1.

of the body fat during fever is due not so much to a direct attack on the fat itself as to the lowering of nutrition and the consequent demand on fat tissues such as occurs in hunger.

Further, it is of interest to know whether the increased heat production during fever is accounted for by the oxidation of such nitrogenous substances as correspond to the increase of nitrogen excreted. It is difficult to decide this accurately, but it is generally assumed (Krehl, Kraus and others) that it is probably sufficient. After all, since the actual increase in heat production is very moderate and in some cases may be very slight indeed, it is easy enough to accept this conclusion, but we are by no means so confident in assuming that the increased heat production does depend solely on the increased nitrogenous decomposition.

The question as to the changes in the proportions of the various nitrogenous substances in the urine brought about by fever is probably a very important one, but our information on this point is not as yet wholly satisfactory. Notwithstanding the fact that the urea output is absolutely increased, the increase in the excretion of other nitrogenous substances may be such that it actually forms a smaller percentage than normal.

Great emphasis was laid by Krehl[53] on the appearance of albumoses in the urine in fever; and there were forms of deutero-albumose which he regarded as particularly characteristic of febrile excretion. Indeed, he carried this idea so far as to assume that the formation of albumoses might furnish the real cause of the febrile reaction, and showed that the injection of such albumoses derived from various sources would cause fever in animals. He has retracted these ideas, however, since it has been shown that the fever thus produced is probably due to impurities, and since it has further been shown, especially by Dietschy,[54] that the occurrence of albumoses in the urine is by no means constant in fever, and that it depends chiefly on the reabsorption of cellular exudates and tissue remains.

Of the other nitrogenous substances the ammonia seems to play an especially important part, being excreted in greatly increased amount in some febrile diseases. Erben[55] records the excretion of 3.53 gm. in one day in a case of measles and Hallervorden[56] and others have recorded daily excretion of 1.75 to 2 gm., although the normal is not more than 0.7. This is doubtless due to the formation of certain organic acid materials in the course of these diseases which demand neutralization by the ammonia set free in the decomposition of the tissues.

There is at times a moderate increase in the excretion of uric acid, although this is by no means a very constant or conspicuous feature of the febrile urine, and, as Horbaczewski pointed out, it depends largely on the amount of destruction of cellular material that has taken place. Thus, we might expect in such a disease as pneumonia, and especially in the epicritical period, an increase in the uric acid output, because of the dissolution of such great quantities of nuclein-holding cel-

53. Krehl and Matthes: Arch. f. exper. Path. u. Pharmakol., 1898, xl, 430. Krehl: Verhandl. d. Cong. f. inn. Med., Wiesbach, 1898, xvi, 229.

54. Dietschy: Inaug. Diss. Basel, 1906.

55. Erben: Ztschr. f. Heil., xxv, 1904, 33-107.

56. Hallervorden: Arch. f. exper. Path., 1880, xii, 237.

lular exudate, but an extensive destruction of any other tissue might be expected to bring about in the same way an increased uric acid output.

Erben points out the fact that both xanthin bodies and amino-acids are increased in fever, but in a degree varying with the character of the disease, for while these substances are increased alike in measles and diphtheria, the amino-acids are much more increased than the xanthin bases in scarlatina and typhoid fever. He explains the prominence of the amino-acids on the basis of the extensive resorption of lymphatic tissue which occurs in those diseases. The following table gives a few of the figures from his extensive investigations, which in the main agree with the earlier ones of von Jaksch.[57]

	Percentage of Nitrogen From					Total Nitrogen g. Per Day.
	Ammonia.	Uric Acid.	Xanthin Bases.	Urea.	Amino-Acids.	
Measles—						
Fever day 9.90	3.23 g	1.39	4.68	77.88	6.15	29.433
Normal day 3.70	per day	1.53	3.86	82.96	7.95	9.79
Scarlatina—						
Fever day 8.66		1.42	2.19	77.98	9.75	9.69
Fever day 10.16		2.81	3.44	71.14	12.17	3.71
Convalescence .. 3.78		1.47	2.33	85.86	6.56	9.07
Typhoid Fever—						
Early in fever... 4.55		1.81	1.14	87.27		14.63
Defervescence .. 2.94		1.46	0.99	77.45	14.71	13.92

A. R. Mandel[58] has studied the excretion of xanthin bases in fevers and finds them markedly increased and inversely proportional to the output of uric acid. He further shows that there is a constant relationship between the height of the fever and the quantity of purin bases in the urine and that a febrile temperature can be produced by the injection of xanthin bases. It seems from this work that we have not reached a position in which we can finally estimate the importance of the metabolism of these substances, but it is probable that their further study will throw much light on the significance of the intensified decomposition and excretion.

Much importance has recently been attached by Folin[59] and others to the excretion of kreatinin in its relation to the nitrogenous metabolism as a whole, and it seemed probable that in such conditions as fever in which there is a great wasting of muscle and other tissues there might be expected an increase in its excretion.

Leathes[60] in his observations on febrile patients in the wards found an actual decrease in the amount of this substance as compared with the normal, but later having kept himself on a kreatinin-free diet he experimented on himself, producing fever by injecting an antityphoid vaccine and then found a definite although slight increase in the amount of kreatinin excreted. Shaffer,[61] on the other hand, does not regard kreatinin as a constant index of endogenous protein katabolism. He finds it slightly increased in acute fevers regardless of the muscular development of the individual. Kreatin also is found by him to be excreted by the subjects of acute fevers, and he thinks that it results from an abnormal breaking down of muscle protein. Van Hoogenhuyze and Verploegh[62] conclude that kreatin may be converted into kreatinin chiefly by the liver and that when the liver is exhausted or injured so that its ability to transform the

57. von Jaksch: Ztschr. f. klin. Med., 1903, l, 67.
58. Mandel (A. R.): Am. Jour. Physiol., 1904, x, 452· 1907, xx, 439.
59. Folin (O.): Am. Jour. Physiol., 1905, xiii, 117.
60. Leathes: Jour. Physiol., 1906-7, xxxv, 205.
61. Shaffer: Am. Jour. Physiol., 1908, xxiii, 1.
62. Van Hoogenhuyze and Verploegh: Ztschr. f. physiol. Chem., 1908, lvii, 161.

kreatin into kreatinin is disturbed, kreatin may also appear in the urine. In several cases they found kreatinin markedly increased during high fever. In the case of one of themselves this was especially clearly demonstrated, as a brief febrile attack occurred during their study of their own kreatinin excretion. Their result differed from that of Leathes in being associated with no great increase in the general nitrogen output.

In addition to the above mentioned substances, there frequently occur in febrile urine one or more of the stages in the oxidation of oxybutyric acid into diacetic acid and acetone. The acetone is that stage which is most likely to appear, and it is only in more intense disturbances of oxidation that the diacetic acid and oxybutyric in turn appear. In convalescence they disappear in a reverse order. These substances are doubtless formed in some such way as they appear in inanition, but practically never reach the abundance in which they are present in that condition. They may be made to disappear in part, at least in some cases, by the administration of carbohydrates. They are not present in fever to any such extent as observed in diabetes, but when a febrile affection supervenes in diabetes the acetone bodies are usually increased. As to the source of these substances, it seems quite probable that they are directly derived from the decomposition of protein material, whether from the inanition which so commonly accompanies fever or from the toxic effects of the infectious process, but they may be an index of the febrile abnormal consumption of fat.

Regnard,[63] Geppert,[64] Minkowski,[65] Kraus[66] and others have shown that in fevers the carbon dioxid content of the blood is diminished and think that this is due also to an acid poisoning which, however, must be somewhat indirectly demonstrated. The increased output of ammonia mentioned above is another indication of the same thing.

CARBOHYDRATES IN FEVER.

With regard to the oxidation of carbohydrates in fever we know very little. There are numerous statements in the literature concerning the disappearance of glycosuria in diabetes when fever supervenes.

Bleiweis[67] showed that this was inconstant and that indeed the assimilation limit for sugar might be lowered in febrile diseases. Richter[68] confirms this inconstancy of the effect of fever on glycosuria and diabetes and also makes the statement that in fever alimentery glycosuria is easily obtained. It can be shown that it is the infection and not the elevation of temperature which stops the glycosuria in diabetes, for the hyperthermy resulting from heat puncture has

63. Regnard: Combustions-Respiration, 1879.
64. Geppert: Ztschr. f. klin. Med., 1880, ii, 356.
65. Minkowski: Arch. f. exper. Path., xix, 209.
66. Kraus: Zeitschr. Heilk., 1889, x, 1.
67. Bleiweis: Centralbl. f. inn. Med., 1900, xxi, 50.
68. Richter (P. F.): Berl. klin. Wchnschr., 1903, xl, 841.

no effect on adrenalin glycosuria, while bacterial infection with fever prevents such glycosuria.

The whole subject of alimentary glycosuria in fever has been considered by Di Campagnolle,[69] who finds that the limit of assimilation of dextrose is markedly lowered. Ott[70] found that in febrile animals the storing and subsequent conversion of glycogen occupied a much shorter time than in normal animals, and he suggests that in man the exhaustion of the stored glycogen may occur more rapidly than in health. Noel Paton[71] also finds from experiments on rabbits that the simple elevation of temperature increases the rapidity with which the glycogen of the liver is converted into glucose, and that in infective fevers the glycogen in the liver is quickly reduced. An interesting paper is that of Hollinger,[72] who studied the sugar content of the blood in health and in fever. The normal content is greatly exceeded in almost all cases of pneumonia which he studied. To such an extent did this hyperglycemia rise that had these cases been diabetics there would certainly have been glycosuria, but none occurred here. In other forms of infection also he finds a similar hyperglycemia.

May and Weber, as we have already mentioned, held to the idea that they could by the administration of carbohydrate during fever reduce protein destruction to, or even below, the normal amount, and, indeed, they were able to reduce the febrile destruction of the body protein to a very great degree. The exact explanation of this is not perfectly clear even yet; whether they merely supplied the deficiency resulting from inanition which would otherwise be supplied by protein, or protected protein from the effect of the hyperthermy alone, or whether finally the carbohydrate given could protect to some extent the protein of the tissues from toxic destruction (which seems entirely improbable) it is difficult to decide. Weber, however, admitted that he was unable in this way to protect the protein completely.

Hirsch, Müller and Rolly, in their studies of topography of heat production, have emphasized the importance of the liver in this process because they found that it was the warmest organ. Hirsch and Rolly[25] investigated the effects of heat puncture on a curarized animal and found that fever could be produced in these animals, which lends support to the idea that the heat production occurs in the liver, and that it depends on the non-nitrogenous metabolism of the liver. It was but a short step to the investigation of the effect of heat puncture in a glyco-

69. Di Campagnolle: Deutsch. Arch. f. klin. Med., 1898, lx, 188.
70. Ott: Deutsch. Arch. f. klin. Med., lxxi, 263.
71. Paton (Noel): Edinburgh Hosp. Rep., 1894, ii, 72.
72. Hollinger: Deutsch. Arch. f. klin. Med., 1907-8, xvii, 217.

gen-free animal, and Rolly[73] found that in such an animal heat puncture is impotent to produce any elevation of temperature. If, however, the glycogen be restored to the animal fever production takes place. Infections, however, give rise to fever in glycogen-free animals quite as well as in those with abundant carbohydrate supply. Senator and Richter[74] repeated this work and found that after making the animal glycogen-free by poisoning with strychnin the heat puncture produces almost as high a temperature as in well-nourished rabbits, and they conclude that the production of fever is not dependent on the presence of glycogen, and, indeed, that hyperthermy does not depend on the burning of any special substance. In my judgment, the positive results of Senator and Richter must have greater weight than the negative results of Hirsch and Rolly, especially in view of the uncertainty which attends the somewhat difficult operation of heat puncture in the production of fever, and we are thus deprived of the brilliant explanation of heat production which Hirsch, Müller and Rolly attempted to furnish us. It seems evident, however, from the other experiments and observations, that carbohydrates are well oxidized in fever, and perhaps even particularly well if we accept the results of Hollinger. At any rate, it appears that in the fevers that have been studied the carbohydrates are rapidly oxidized and may even protect to a certain degree the proteins which are otherwise so quickly attacked, and we may the more readily assume that in the later stages of fever in which no great quantity of carbohydrates has been given in the food the oxidation finally depends chiefly on the protein and fat.

WATER METABOLISM IN FEVER.

As to the water exchange we again have rather conflicting ideas which doubtless depend on inaccuracy of observation and on complications which are not necessarily found in all febrile affections. Such complications may arise as is obvious from disease of the kidneys or of the heart or from general disturbances of the mineral metabolism which depend on degenerative processes in the tissues as a whole. Here, again, it is the water balance which must be accurately determined so that the observations of Glax,[75] who neglected the respiration, perspiration, etc., and decided on water retention in fever, can hardly be considered. Somewhat more exact are the investigations of Riva Rocci and Cavallero,[76] who weighed their patients and estimated the respiratory exchange, and

73. Rolly: Deutsch. Arch. f. klin. Med., 1903, lxxviii, 250.
74. Senator and Richter: Ztschr. f. klin. Med., 1904, liv, 16.
75. Glax: Berl. klin. Wchnschr., 1894, xvi, 937.
76. Riva Rocci and Cavallero: Deutsch. med. Wchnschr., 1895, xxi, 529.

thus calculated the water excretion from the skin and lungs. They found a variable retention during fever, but a great output of water at the end of fever. Krehl and Matthes found that the heat loss in fever from evaporation preserved its relation to the heat loss by radiation and conduction—an abnormal condition—because in health the heat loss by evaporation is extraordinarily variable and after muscular exertion the increase is enormous in comparison to that by radiation and conduction. Wassilewsky[77] finds in the study of many febrile diseases that the evaporation from the skin is very low during the stage of increment of the fever, somewhat higher but still below the normal during fastigium, but greatly increased in the stage of decrement. Lang[78] experimented with tuberculin fever and found that there was a marked difference in fever between the evaporation of water by the lungs and by the skin, for, while in health the excretion by the skin per square meter may be 13 gm. per hour, increasing 100 per cent. after an abundant meal and very much more after muscular work, it is also about 13 gm. during the height of fever. On the other hand, the normal man exhales 0.21 gm. per kilo from the lungs and 0.27 after a meal. The febrile patient may exhale while fasting 0.32 gm. per kilo from the lungs. Thus in fever the evaporation from the lungs is increased 50 per cent. and the total loss of water is 20 per cent. Thus the insufficiency of the evaporation from the skin in fever must have a very important rôle in the elevation of the temperature. It must be suggested, however, that in this work of Lang only one type of fever is considered, whereas it is well known that in certain other types, such as that seen in tuberculosis and acute rheumatism, there may be a great deal of sweating associated with high fever.

Schwenkenbecher[79] has devoted much attention to the water exchange in fever and finds that the excretion of water varies perhaps more with the "direction" of fever, as he expresses it, than the actual height of temperature. He finds that in pneumonia there is, on the whole, no marked retention of water, although that is usual in typhoid fever and tuberculosis in the sense that, although the patient loses more water than the healthy person, he also excretes more solid substance and may become relatively water rich. He follows Liebermeister in his ideas of heat regulation, finding that the febrile person with his elevated temperature excretes water when the heat production is still further

77. Wassilewsky: Perspiratio insensibilis im Fieber, Diss., Petersburg, 1867.
78. Lang: Deutsch. Arch. f. klin. Med., 1904, lxxix, 343.
79. Schwenkenbecher: Arch. f. exper. Path., 1905, liii, 365; 1906, liv, 168; 1907, lvii, 285.

elevated by a meal, in the same proportion as the normal person. The amount of water at the command of these mechanisms is very considerable, so that until we have more accurate knowledge of the water balance we can not certainly assume that the diuresis which accompanies the crisis in certain fevers is dependent on a previous active retention of water. It is clear that these observations of Schwenkenbecker and Lang and others give us information only as to the alterations of the water exchange which have to do with heat regulation, while the total water metabolism is not elucidated by this means. For that purpose we must have such absolute figures as are to be found in Staehelin's table, from which we learn that the dog infected with surra took in during the whole period with the food and drink 9,030 gm. of water and excreted altogether 11,225 gm., the water of urine, feces and respiration being measured. The dog thus lost during this period 2,195 gm. of water, which, in spite of the fact that some edema developed, does not argue for the retention of water.[80] On the whole, while the diminution in the urinary output during the height of fever and the concentration of the urine are well known in contrast to the increased urinary output at the crisis or in the early days of convalescence, the attempts made to demonstrate, in consequence of this, increased water content of the blood and tissues have not been distinctly successful or convincing. The explanation of the decrease in the amount of urine has generally been attempted on the basis of disturbances in the blood pressure and pathologic changes in the kidneys interfering with their function. It seems, however, that in view of the sudden restitution of the functional activity of the kidneys in the crisis, the disturbance must have been a functional one rather than an actual anatomic lesion, and one can hardly escape the idea that if water is retained in the body during fever it is not because of the inability of the kidneys to excrete it, but rather because it is needed in the tissues to serve some good end in the furthering of the febrile reaction. Much more accurate work is needed for the clearing up of this subject.

MINERAL METABOLISM IN FEVER.

Of the metabolism of mineral salts in fever we can speak with certainty only of the relation of the sodium chlorid. A distinct retention

80. In another paper[81] Staehelin intimates the effect of night sweats in tuberculous patients and finds that sweat as such has no influence on the consumption of energy and has not nearly the cooling effect that might be expected, and that its significance, therefore, must be sought elsewhere than in the heat regulation.

81. Ztschr. f. klin. Med., 1908, lxvi, 241.

of the sodium chlorid in the tissues seems to occur in certain febrile diseases, although not in all. Redtenbacher[81] was the first to point out such chlorid retention in pneumonia, and his discovery has been abundantly confirmed by Röhmann,[82] Terray,[83] Moraczewski,[84] Hutchinson[85] and many others. It is found that the amount of sodium chlorid excreted in the urine in pneumonia is very greatly decreased until the crisis, when it is excreted in large amounts. This is true even though an increased amount of salt be given in the food. Röhmann thought that the retention was due to a combination of sodium chlorid with circulating proteins in the blood, but this has been disproven, and it is shown that the accumulation really takes place in the tissues. Leyden, who emphasizes the retention of water during fever, held the view that the retention of chlorids was for the purpose of maintaining the isotonicity of the tissue fluids, and in this Terray agreed, but it seems, as Hutchinson points out, that the amount retained is far greater than is necessary for that purpose, and some other explanation must be found. This is the more difficult, since other fevers, such as typhoid, show no such constant chlorid retention. Another suggestion is that the chlorids actually forming a constituent of the excessive exudation in pneumonia may explain the retention, but even this, as Terray has shown, is quite insufficient to account for the amount retained. In malaria it has been found by Rem Picci and Caccini[86] and also by Terray that the chlorid retention is to be observed on the fever-free days, while there is an increased output on the days of fever, and they think that the great destruction of red corpuscles is sufficient to account for this—again an improbability.

We know so little about the excretion of other mineral substances in fever that we can hardly resort to the consideration of the balance usually maintained between these substances in order to explain the divergence from normal in the relation of the chlorids. It may have a direct relation to the excretion of phosphates, as Schwartz thought. There is a great deal of dispute about phosphorus excretion in fever, but Moraczewski tells us that the phosphorus excretion is increased, especially with respect to the acid phosphates. The relation between the phosphorus excretion and that of the calcium is well known to be intimate, and it is stated that the calcium excretion is diminished in fever, but that

82. Redtenbacher: Wien. med. Ztg., 1850, 373.
82. Röhmann: Ztschr. f. klin. Med., i, 543.
83. Terray: Ztschr. f. klin. Med., 1894, xxvi, 341.
84. Moraczewski: Ztschr. f. klin. Med., 1899, xxxix, 44.
85. Hutchinson: Jour. Path. and Bacteriol., 1898, v, 406.
86. Rem Picca and Caccini: Policlinico, 1894, 564; Maly's Jahresb., 1894, xxiv, 57.

after convalescence this retention of calcium phosphate is compensated for by an increased excretion. Perhaps the most satisfactory paper on the subject is the recent one by Moraczewski,[87] in which cases of pneumonia, typhoid, malaria and tuberculosis are studied. All the assertions of the earlier writers are confirmed as far as they go, and in pneumonia a very distinct critical rise in the phosphorus and potassium excretion is noted, the excretion of these substance remaining high after the crisis, while the chlorids are extremely low until several days after the crisis, when they suddenly increase. Moraczewski gives a scheme to illustrate the relations of chlorids and phosphorus to the temperature curve, which he divides into several periods. The onset of the fever brings with it an increase of chlorids, decrease of nitrogen and decrease of phosphorus. In the second period the chlorids decrease, nitrogen increases and phosphorus decreases, but begins to rise a little later with the nitrogen. From this condition, in which the chlorids fall very low, there occurs a change with the fall of temperature which consists in a continued increased output of nitrogen and of phosphorus, while the chlorids increase to normal or above it, all finally returning to normal.

Let us now, after this somewhat wearisome discussion of the details of the metabolism in fever, review very briefly what has been said about the whole subject. We find that in fever we have a reaction which is occasioned by a variety of injurious influences acting on the body, a reaction which is characterized by a moderate increase in the oxidative processes, and consequent moderate increase in heat production, but more especially characterized by such changes in the heat regulation as lead to disproportion between the heat production and the heat loss, and a consequent rise in body temperature. The disturbances in metabolism are found to consist, not especially in the oxidation of non-nitrogenous substances which are predominantly concerned in health in the production of heat, but in much greater degree in the destruction of protein material, not the protein of the food exclusively, but in a pre-eminent degree the protein of the tissues. The destruction and oxidation of carbohydrate and fat goes on in fever also, possibly to a greater extent than has generally been supposed. The changes in mineral metabolism are as yet but imperfectly understood, but it appears that in the course of fever water and certain mineral salts are at times retained in the body only to be excreted later when the febrile process is over. On the whole, the change in metabolism is not one particularly marked by its intensity, but rather by the peculiar proportions in which the materials are concerned, and the formerly accepted idea that there we have to deal with a greatly increased oxidation is upheld neither by the amount of heat production nor by the quantity of oxidation products resulting. It seems from the constancy of the characters of the febrile reaction, no matter what the exciting cause of the fever be, that we can not regard it

87. Moraczewski: Virchow's Arch. f. path. Anat., 1899, 155.

as the mere effect of the injurious agent on the passive body, but must rather look on it in the light of an elaborate modification of chemical processes evolved in the course of centuries of development to answer some special purpose. It seems probable that every detail of this reaction is that which is best calculated to take its own special part in the making up of a whole well-aimed plan. Every available mechanism cooperates to the uttermost of its power in the first stage to elevate the temperature of the body; when that temperature is once brought to a suitable level, many of these mechanisms are no longer necessary, and when the febrile temperature itself is no longer needed other mechanisms are equally active in discharging the heat. The aim of the individual peculiarities of metabolism is not so easily grasped, but it is here again quite as difficult to escape from the conviction that they are designed to play their part in the general plan, and because this reaction has developed in the long processes of evolution, it seems inevitable that this plan is one devised for the good of the organism, and that fever is in its essentials a protective reaction. This idea is not by any means new, but has prevailed for centuries, being lost throughout whole periods in the struggles of physicians to cure the fever regardless of the disease, and it is only in recent years that it has again become usual to think of the fever as probably a beneficial reaction which should not be interfered with.

Some light has been shed on this by the controversies regarding the usefulness of antipyretics, about which a very considerable literature has sprung up. In just what way the fever acts beneficially it is almost impossible to say in the present state of our knowledge, but the recent studies of the development of immunity, which show that when the tissues are attacked and injured they react by developing an immunizing substance, probably offer a general explanation for the type of reaction with which we are dealing, which agrees in so many particulars with the behavior of the organism in the known development of immunity. The very facts that when the injury is overwhelming we may have no febrile reaction, and that when the course of the intoxication suddenly changes to the advantage of the organism the fever ceases, point to a close analogy between the febrile process and the process of the production of immunity. Why the heightening of the temperature of the body should be necessary is not perfectly evident, but it is easy to believe that under those circumstances the production of immune substances might proceed in a way impossible at a lower temperature. In conclusion, then, I can

only express my conviction that the febrile process is a reaction beneficial to the organism and doubtless intimately associated with the development of protective substances to combat the injurious agencies which have invaded the body.[88]

88. Since the delivery of this lecture there has appeared the very interesting paper of Rolly and Meltzer (Deutsch. Arch. f. klin. Med., 94, 1908, 335) on the significance of hyperthermy. They find the growth of bacteria somewhat inhibited by temperatures of 40-41 C. No certain result could be obtained as to the protective effect of overheating on animals infected with bacteria when large quantities are injected at once. If, however, smaller quantities are injected daily there is a distinctly favorable influence. Heating alone does not change the alexin content of the blood, and the effect of heating on phagocytosis is indefinite in the animal, but up to 40 C. is apparently favorable *in vitro*. Heating has no influence on the resistance of animals to fatal doses of a bacterial poison, but when small doses are given agglutinins and bacteriolytic substances are produced far more rapidly and abundantly in animals which are kept overheated than in those which are kept cool.

The febrile temperature injures the organism to a certain extent by causing loss of weight, lowering the hemoglobin index, etc., but there are no definite injuries produced in the organs even by a long heating. Even though overheating can not be regarded as surely identical with the condition in fever, it is probable that this paper marks a most important advance in the comprehension of the true nature of fever.

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